DOI:
10.1016/j.msard.2016.10.003

Document Version
Peer reviewed version

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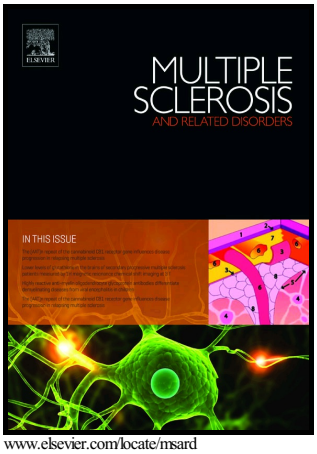

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PII: S2211-0348(16)30179-1
DOI: http://dx.doi.org/10.1016/j.msard.2016.10.003
Reference: MSARD478

To appear in: *Multiple Sclerosis and Related Disorders*

Received date: 3 August 2016
Revised date: 5 October 2016
Accepted date: 10 October 2016

Cite this article as: Ellen Butler, Faith Matcham and Trudie Chalder, A Systematic Review of Anxiety Amongst People with Multiple Sclerosis, *Multipl Sclerosis and Related Disorders,* http://dx.doi.org/10.1016/j.msard.2016.10.003

A Systematic Review of Anxiety Amongst People with Multiple Sclerosis

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Abstract

Background

Multiple Sclerosis (MS) is a chronic neurological disease, which poses significant psychological challenges. The purpose of this systematic review was to identify factors that are associated with anxiety in people with MS (PwMS). It aimed to examine the strength of evidence for factors associated with anxiety symptoms and identify limitations of existing studies.

Method and Results

One hundred and thirty one studies met inclusion criteria and were included in the review. A narrative synthesis was then conducted. Anxiety was found to be associated with a variety of demographic, physical, psychological, cognitive and social factors. A consistent finding was that anxiety was strongly associated with both high level of disability and low quality of life. A strong association between anxiety and depression was also found.

Conclusion

Implications for these results are discussed and a preliminary model of understanding anxiety in the context of MS is outlined. Given the overlap between anxiety and depression a transdiagnostic treatment approach is suggested. In light of the shortcomings of extant studies, suggestions for future research are offered.

Key words
Anxiety, Multiple Sclerosis, Systematic review

Abbreviations
MS: Multiple Sclerosis
PwMS: People with Multiple Sclerosis

1. INTRODUCTION

Multiple Sclerosis (MS) is a chronic inflammatory neurological condition of the central nervous system(DeLuca, Genova, Hillary, & Wylie, 2008). The illness occurs when the protective myelin sheath of nerve fibers in the brain and spinal cord become damaged, disrupting the transfer of messages from the brain to other parts of the body (National MS Society, 2012). There are various types of disease courses including: a benign course, a relapsing-remitting course (RR), which often progresses into a secondary progressive course (SP); and a type that is progressive from its onset (PP)(NHS Choices, 2013). Due to the unpredictability of the course of the illness, and the lack of treatments available, the main goals of intervention are usually to delay progression, relieve symptoms and treat any mental health issues that arise (Burks, Bigley, & Hill, 2009). Mental health problems, such as depression and anxiety, have been found to be particularly common among people with Multiple Sclerosis (PwMS) (Janssens et al, 2003) and to date most of the literature has focused on depression in PwMS. This study therefore aims to broaden current knowledge by focusing exclusively on the role of anxiety in PwMS.

Anxiety can be defined as an excessive feeling of unease and worry which individuals find difficult to control, and consequently interferes with everyday

functioning (American Psychiatric Association, 2000). For PwMS, anxiety may be severe and prolonged due to the individual's concern about the uncertain outcome of future episodes and the potential seriousness of the symptoms (Cecile et al., 2004). Worldwide estimates of the proportion of the population who are likely to suffer from anxiety in their lifetime range between 0.8% and 6.4%(Kessler & Wang, 2008). However, for PwMS, anxiety has been found to affect between 15.8% and 57% of the population (Feinstein et al, 1999; Garfield et al, 2012). Anxiety is amongst the most important factors to investigate for PwMS as, if untreated, it can significantly impact quality of life, treatment adherence and symptoms(Mohr & Cox, 2001). Therefore, it is widely agreed that identification of symptoms and treatment should be introduced at the earliest opportunity (Dahl et al, 2009). However, current knowledge of anxiety and its treatment in PwMS is limited by the lack of research on why PwMS experience anxiety.

The purpose of the current review is to systematically identify existing literature that focused on anxiety among PwMS. The aims are a) to gain an overview of the strength of evidence for factors associated with anxiety in the context of MS b) to identify methodological problems, gaps within the literature and directions for future research. A reliable overview of the field of research is likely to help clinicians improve the wellbeing of PwMS and to gain a greater understanding of factors that are linked to anxiety so that these could be targeted within interventions.

2. METHOD

2. 1. Search Strategy and Selection Criteria

The systematic review protocol and data extraction forms were designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)(Moher, Liberati, Tetzlaff, Altman, & Group, 2009). Electronic databases (MEDLINE, EMBASE, Web of Science, BIOSIS, KCI, SciELO, CINAHL and Psychinfo) were searched for studies between January 1980 and September 2016 (see Appendix A for search terms). The screening

process then took place which involved: removing duplicates; title screening; excluding irrelevant titles; abstract screening; then full-text assessment against eligibility criteria.

2. 2. Inclusion and Exclusion Criteria

Cross-sectional and prospective studies were included that were published empirical quantitative research reports examining anxiety in PwMS. Intervention studies were not included in this review as data collected in randomised trials may not be applicable to the wider population of patients because trials use such rigorous inclusion criteria to get an artificially homogenous group of patients (Rothwell, 2005). The review included all available studies that identified clinically relevant anxiety, i.e. anxiety severe enough to warrant clinical intervention that was measured by clinical judgment or a validated, appropriate multi-item measure. Single item measures were excluded due to their vulnerability to random measurement errors and lack of internal consistency reliability (Hoeppner, Kelly, Urbanoski, & Slaymaker, 2011). The factors associated with anxiety were examined. Prevalence estimates were also obtained for Generalised Anxiety Disorder (GAD), Obsessive Compulsive Disorder (OCD), Post-traumatic Stress Disorder (PTSD) and Social Anxiety. Ambiguities as to whether a study met the inclusion criteria were resolved through discussion between the authors (EB and TC).

2. 3. Data Extraction

Study titles were screened first, followed by abstracts by a research assistant in collaboration with the primary researcher (EB). The full texts were then screened by EB and all ineligible papers were excluded. Information for each eligible study was extracted and tabulated. Extracted data included sample characteristics, type of analysis, relevant measures, main findings, demographics and information for quality assessment. The extraction process was completed independently by EB and any disagreements were resolved through discussion of the study with TC. It was decided that abstracts without

full articles would be included given that many met inclusion criteria and appeared relevant to the research question.

2. 4. Synthesis

A narrative synthesis was conducted in line with previously described methods (Popay et al., 2006). Full reference information for included studies can be found in Table 1 and 2 and appendix C. Factors relating to anxiety were grouped into overarching conceptually or thematically related categories. The importance of each factor was accounted for by combining a count of the studies that identified or did not identify significant relationships while considering their methodological quality. Patterns in the data were examined and potential sources of heterogeneity between studies were explored including moderators of results such as sample size. Discrepancies, uncertainties and unanswered questions within the studies were also analysed.

Table 1: Cross Sectional Studies

Authors, Year	Multi-Centre	Type of MS	Measure of anxiety	Other measures used	Gender/Age	Full paper	Eligibility Criteria Specified	Powered	Recruitment strategy
Akbar, N., et al. (2011)	no	Definite MS	HADS	MSNQ, NEO-FFI,	81 females /27 males av. 45 years	yes	yes	no	Convenience sampling
Al-Asmi, A., et al. (2013)	no	Definite MS (McDonald criteria)	HADS	EDSS	41 females/ 16 males. av. 31.4 years	yes	yes	no	Consecutive
Aloulou, J., et al. (2011)	no	Definite MS	HADS	TAS-20	18 females /13 males av. 39 years.	no	yes	n/s	n/s
Anhoque, C. F., et al. (2011)	no	14 RRMS, 3 SPMS, 2 PPMS	BAI	BDI	14 females /5 males. av. 37 years.	yes	yes	no	Consecutive
Askari, F., et al. (2014)	no	142 RRMS, 38 SPMS	BAI	BDI, EDSS	151 females /29 males, av. 32.4 years	yes	yes	no	Consecutive
Bamer, A. M., et al. (2008)	yes	Definite MS	HADS	PHQ-9	1034 females/ 237 males.	no	n/s	n/s	n/s

Beier, M., et al. (2013)	n/s	Definite MS	PHQ-A	None Specified	av. 50.9 years 421 females/ 92 males	no	n/s	n/s	n/s
Beiske, A. G., et al. (2008)	yes	Clinically Definite MS (without severe cognitive impairment, psychiatric impairment or other serious disabling disease)	HSCL-25	PASAT, MS-FS	94 females / 46 males av. 30.9 years	yes	yes	no	Consecutive
Bogart (2015)	Yes	Self-report diagnosis MS	HADS	Disability Personal Identity Scale, ADL	48 females, 58 males av.=58.3 years	Yes	Yes	No	convenience
Brajkovic, L., et al. (2009)	no	Definite MS	HADS	MSQLI, COPE PSWQ, CMDI, EDSS, FIS, BPI, SILS, SRT, SDMT, Visual Elevator subtest. Memory questionnaire, DES-11, NEO-FFI, BDI-FS, neuropsychological tests	51 females/ 17 males	no	n/s	n/s	n/s
Bruce, J. M. & P. Arnett (2009)	yes	RRMS, SPMS	STAI		42 females/ 8 males av. 46.2 years	yes	yes	no	n/s
Bruce, J. M., et al. (2009)	no	RRMS, SPMS	STAI		71 females/ 8 males. av. 45.4 years	yes	yes	no	n/s
Bruce, J. M. & Lynch, S. G. (2011)	no	MSRR, MSSP, MSPP	STAI		74 females /11 males. av. 47.12 years	yes	yes	no	n/s
Chalfant, A. M., et al. (2004)	yes	MSRR, MSSP, MSPP	Clinician Administered PTSD scale	GDS, DSQ	45 females /13 males av. 49.6 years	yes	no	no	n/s
Chalk, H. M. (2007)	yes	Definite MS	BAI	EDSS, CMSS, CAHS, SSQ, SWLS, CES-D, BAI-PC, MHI	266 females /63 males	yes	yes	no	Randomised
Chylova, M., et al. (2009)	n/s	Definite MS	HADS	SF-36, EDSS	150 female/73 males. av. 38.9 years	no	n/s	n/s	n/s
Cihelkova, S. & Bojar, M. (2009)	n/s	Definite MS	BAI	BDI II, SCL-90, MMSE, EDSS	25 females /15 males	no	n/s	n/s	n/s
Counsell, A., et al. (2013)	yes	Definite MS - 61.1% RRMS,	HADS; PTSD Checklist	MSIS-29	99 females/ 27 males.	yes	yes	no	Randomised

		17.5% SPMS, 7.9% PPMS, 3.2% PPMS, 3.2% benign type, 4.8% were unsure of type.			av. 45.5 years				
Curral, R., et al. (2011)	no	Definite MS 80.4% RRMS, 9.9% SPMS, 9.6% PPMS	HADS	MMSE, Raven, MOS SF-36, SCL-90, EDSS	35 females /13 males	no	n/s	n/s	n/s
Da Silva, A. M., et al. (2011)	no		HADS	EDSS, MSSS	214 females/ 111 males av. 39.5 years	yes	yes	no	Consecutive
Dahl, O.-P., et al. (2009)	yes	Definite MS	HADS	FSS	111 females /61 males av. 50.1 years	yes	yes	no	Convenience
Dubayova, T., et al. (2013)	yes	Definite MS	HADS	PCS, MCS, EDSS, UDPRS	154 females /44 males. av. 67.6 year	yes	yes	no	Randomised
Espinola-Nadurille, M., et al. (2010)	no	Definite MS (McDonald criteria) - 75.6% RRMS, 18.9% SPMS, 5.4% PPMS	HADS	DSM, MADRS	24 females / 13 males av. 36.3years	yes	yes	no	Consecutive
Etesam et al (2016)	Yes	n/s	HADS	DDI, EDSS	n/s	No	No	No	n/s
Farrell, E., et al. (2011)	no	Definite MS	HADS	MSNQ	n/s	no	n/s	n/s	n/s
Feinstein, A., et al. (1999)	no	Definite MS (Posars criteria)	HADS	GHQ-28	107 females /45 males av. 44.98 years	yes	yes	no	Consecutive
Fisk, J. D., et al. (2014)	yes	Definite MS	HADS	EDSS, HUI, HRQoL, D-FIS	714 females/ 235 males av. 48.6 years	no	n/s	n/s	n/s
Foroughipour, M., et al. (2012)	no	Definite MS	Y-BOCS	EDSS DSM	84 females/ 28 males. av. 31.9 years	yes	yes	no	Consecutive
Fruhwald, S., et al. (2001)	no	Definite MS	ZARS	EDSS, MMSE, ZDRS	57 females/ 17 males. av. 39.8 years	yes (German)	yes	no	n/s
Garfield, A.	yes	Definite	HADS	EDSS, GHQ-	41	yes	yes	no	Randomi

C. & Lincoln, N. B. (2012)		MS- 35 MSRR, 10 MSPP, 20 MSSP, 3 Benign.		12, GNDS, MHLC, MSSS,	females / 27 males av. 50 years			sed
Glanz, B. I., et al. (2012).	no	RRMS	STAI	MSQOL-54, CESD, MFIS, STAI, SDMT	287 females/ 90 males. av. 45.4 years	yes	yes	no	Consecu tive
Goretti, B., et al. (2014).	yes	RRMS	STAI	BRB, BDI BDI-II,	140 females / 50 males av. 37.5 years	yes	yes	no	Consecu tive
Grech et al (2015)	No	RR or SPMS (McDona ld criteria)	STAI	MSQOL-54, Daily Hassles Scale, measures of cognition	83 females, 24 men av.=48.8 years	Yes	Yes	No	Conveni ence
Hakim, E. A., et al. (2000).	yes	Definite MS 50	HADS	EDSS, MI	Male: female ratio- 1:2.1. av. 48.3 years	yes	yes	no	Consecu tive
Harding, K. E., et al. (2012).	n/s	RRMS, 39 SPMS.	GHQ30	EDSS, GHQ30 HAM-D,	80 females / 22 males	no	n/s	n/s	n/s
Ionescu, P., et al. (2012).	n/s	Definite MS	HAM-A	EDSS, QOL, IADL	n/s	no	n/s	n/s	n/s
Iriarte, J., et al. (2000).	no	Definite MS	HAM-A	FDS, FSS, HRSD EDSS	105 females / 50 males. av. 32.6 years	yes	yes	no	Consecu tive
Janssens, A., et al. (2003).	yes	Definite MS	HADS	SF-36, IES	71 females/ 30 males. av. 37.5 years	yes	yes	no	n/s
Janssens, A., et al. (2004).	yes	Definite MS	HADS	EDSS, IES	71 females/ 30 males. av. 37.5 years	yes	yes	no	n/s
Jones, K. H., et al. (2012)	yes	14.4% PPMS, 61.7% RRMS, 9.4% SPMS, 14.5% unsure	HADS	None specified	2941 females/ 1237 males. av. 50.9 years	yes	yes	no	Conveni ence
Jones, K. H., et al. (2013)	yes	Definite MS	HADS	MSIS-29, EQ5D	n/s	no	n/s	n/s	n/s
Jones, S. M. & Amtmann, D. (2014)	yes	Definite MS - 58.8% RR, 11.1% PP, 20% SP, 1%PR	PROMIS	Neuro-QOL, EDSS	280 females/ 125 males av. 52.68 years	yes	yes	no	Conveni ence
Jones, K. H., et al. (2014)	yes	Definite MS-	HADS	MSIS-29	3211 females/	yes	yes	no	Conveni ence

		14.8% PPMS, 62.1% RRMS, 8.1% SPMS, 14.9% unsure			1305 males. av. 50.7 years				
Jopson, N. M. & Moss-Morris, R. (2003)	yes	Definite MS	HADS	SIP-68, FSS, RSES, IPQ-R	131 females/ 37 males. av. 56.2 years	yes	yes	no	Convenience
Julian, L. J. & Arnett, P. A. (2009)	yes	Definite or probable MS (Posar criteria)	STAI	Neuropsychological measures of executive functioning, CMDI	61 females/ 16 males. av. 46.58 years,	yes	yes	no	Convenience
Karadayi, H., et al. (2014)	no	Definite MS (McDonald criteria)	HAM-A	GAF, FSS, EDSS MMSE, Cognitive measures	21 females/ 10 males av. 38.3 years	yes	yes	yes	n/s
Kehler, M. D. & Hadjistavropoulos, H. D. (2009)	yes	Definite MS	HADS	CHIP, GNDS	201 females/ 45 males. av. 41.82 years	yes	yes	no	Convenience
Kikuchi, H., et al. (2013)	yes	Definite MS	NAS-J	EDSS, FAMS	118 females / 45 males av. 31.9 years	yes	yes	no	n/s
Korostil, M. & Feinstein, A. (2007)	no	Definite MS	HADS	BSS, SSSI, Neuropsychological Screening Battery	104 females/ 36 males. av. 43.9 years	yes	yes	no	Consecutive
Kostaras, P., et al. (2008)	n/s	Definite MS	STAI	SDMT, BDI	n/s	no	n/s	n/s	n/s
Kraft, G. H., et al. (2012)	no	Definite MS	PROMIS	Quality of life indicator	n/s	no	n/s	n/s	n/s
Krokavcova, M., et al. (2010)	yes	Definite MS	HADS	SF-36, EDSS	122 females/ 62 males. av. 40.5 years	yes	yes	no	Convenience
Labuz-Roszak, B., et al. (2007)	no	n/s conference paper	HADS	FSS, ESS, AIS, MADRS	87 females /35 males av. 37.7 years	no	n/s	n/s	n/s
Leonavicius, R. & Adomaitiene, V. (2013)	no	Definite MS. Progressive- 182, RRMS-130	HADS	EDSS, ICD-10	196 females /116 males. av. 42.01 years	yes	yes	no	n/s
Leonavicius, R. & Adomaitiene, V. (2011)	yes	MSRR, Progressive MS	HADS	EDSS, ICD-10	187 females /83 males av. 42.42 years	no	n/s	n/s	n/s
Leonavicius, R. & Adomaitiene, V. (2014)	no	RRMS	HADS	MOSS, HRQoL	86 females/ 51 males. av.	yes	yes	no	n/s

					42.01years				
Lester, K., et al. (2007)	no	MSRR, MSPP, MSSP	HADS	EDSS, MSIS-29, Self-efficacy for managing chronic disease, Neuropsych screening questionnaire	62 females/ 18 males. av. 44 years	yes	yes	no	n/s
Levinthal, D. J. & Bielefeldt, K. (2014)	no	Definite MS	HADS	MSIS-29, PAGI-SYM, PAGI-QOL, PHQ-15	n/s	no	n/s	n/s	n/s
Liu, X. J., et al. (2009)	no	Definite MS	SCL-90	LES, EPQ,SSRS	26 females /15 males. av. 37.44 years	yes	yes	no	Consecutive
Lopes, J., et al. (2012)	n/s	Definite MS	HADS	EDSS, FSS	88 females/ 31 males. av. 42 years	no	n/s	n/s	n/s
Maia, D., et al. (2011)	n/s	Definite MS	HADS	LNNB, FACE-111	25 females	no	n/s	n/s	n/s
Marrie, R. A., et al. (2013)	yes	Definite MS	ICD Diagnosis. Determined by a psychiatrist	ATC	3006 females/ 1186 males	yes	yes	no	Consecutive
Medin, K. L., et al. (2014)	n/s	Definite MS	None Specified		n/s	no	n/s	n/s	n/s
Middleton, L. S., et al. (2006)	no	Definite MS (McDonald criteria)	SAS	Cognitive tests, CFQ, FFS, CES-D, EDSS	163 females / 58 males av. 44.8 years	yes	yes	no	Consecutive
Milanlioglu, A., et al. (2013)	n/s	RRMS and SPMS	POMS	EDSS, COPE	36 females /14 males	yes	yes	no	Consecutive
Milinis, K., et al. (2014)	yes	Definite MS	HADS	WHOQOL-BREF, LMSQOL, WHODAS, MSSS-88, NRS 0-10, NFI-MS, NPS	n/s	no	n/s	n/s	n/s
Miljatovic, A. M. (2013)	no	Definite MS	HAM-A	HAMD-17, EDSS	n/s	no	n/s	n/s	n/s
Mills, R. J. & Young, C. A. (2011)	yes	Definite MS	HADS	NFI-MS, ESS, MSIS-29	451 females/ 184 males av. 46.6 years	yes	yes	no	n/s
Montel, S. R. & Bungener, C. (2007)	no	Definite MS (Posars criteria)	HAM-A	MINI, MADRS, EHD, FABWCC, CHIP, SEP59	89 females /46 males. av. 44 years	yes	yes	no	n/s
Morrow, S. A., et al. (2014)	no	Newly diagnosed	HADS	FSS, BDIFS	70 females/ 26 males. av. 36.9 years	no	n/s	n/s	n/s
Nicholl, C. R., et al.	no	Definite MS-	HADS	GHQ, EADL, CORE, BSI,	70 females/	yes	yes	no	Consecutive

(2001)		14% MSRR, 45% MSPP, 19% MSPP		GNDS, BDI	26 males. av. 48.97 years				
Niino, M., et al. (2012)	n/s	Definite MS	NAS-J	EDSS, FAMS	n/s	no	n/s	n/s	n/s
Noy, S., et al. (1995)	yes	RRMS	HAM-A	HRSD, Hackett-Cassem Denial Scale, MAACL-R, EDSS	15 females /5 males. av. 41.8 years	yes	yes	no	Consecutive
Ostacoli, L., et al. (2013)	no	Definite MS-90.8% MSRR, 3.02% MSPP, 6.9% MSSP	HADS	IES-R, DSM, FSS	164 females / 68 males av. 41.29 years	yes	yes	no	Consecutive
Paredes, S. & Kirchner Nebot, T. (2012)	yes	Definite MS	SCL-90-R (Spanish)	SCL-90-R	62 females /28 males. av. 38.58 years	no	n/s	n/s	n/s
Pfaff, L., et al. (2014)	n/s	RRMS	HAM-A	EHD, TAS 20	16 females	no	n/s	n/s	n/s
Pieper, L., et al. (2012)	yes	Definite MS	DSM-IV	UNDS, LOT-R	n/s	no	n/s	n/s	n/s
Poder, K., et al. (2009)	no	Definite MS	SPIN, HADS	HUI, EDSS	201 females/ 44 males. av. 46.1 years	yes	yes	no	Consecutive
Poder, K., et al. (2007)	no	Definite MS 66% RRMS, 12% PPMS, 9%	SPIN,	EDSS, HUI	216 females/ 49 males	no	n/s	n/s	n/s
Reade, J. W., et al. (2012)	yes	SPMS, 13% other	MHI	MSQOL-54, MOS	112 females/ 33 males	yes	yes	no	Randomised
Roy Bellina, S., et al. (2010)	n/s	Definite MS	HAM-A	IPQ-R, BDI, TAS-20	26 females /6 males. av. 40 years	no	n/s	n/s	n/s
Roy-Bellina, S., et al. (2009)	n/s	Definite MS	STAI	EDSS, MHKC, SSQ, WCC, IPQ-R, BDI-11	34 females /11 males av. 45 years	no	n/s	n/s	n/s
Sarisoy, G., et al. (2013)	no	Definite MS	STAI	SCL-90-R, BDI, PSQI, Padua Inventory, SES, EATS-26, EDSS	56 females /20 males av. 37.84 years	yes	yes	no	Convenience
Schwartz, C. E., et al. (1996)	no	Definite MS	Anxiety subscale on AIMS	MAF, EDSS, SIP, Rao cognitive battery, the Trailmaking Test, depression and social activity limitations	101 females /38 males av. 43.06 years	yes	yes	no	Inclusive

				subscales from AIMS, Ryff Happiness Scale.					
Shabani, A., et al. (2007)	yes	Definite MS	DSM interview	None Specified	45 females /40 males av. 47. 6 years	yes	yes	no	Randomised
Sidorenko, T., et al. (2010)	no	Definite MS	HADS	EDSS	n/s	no	n/s	n/s	n/s
Silva, A., et al. (2009)	n/s	171 RRMS,25 SPMS, 24 PPMS	HADS	EDSS, MMSE	150 females /81 males. av. 39.94 years	no	n/s	n/s	n/s
Silva, A. M., et al. (2011)	n/s	Definite MS (minimum 10 years disease duration)	HADS	EDSS, FAMS	103 females /56 males av. 44.45 years	no	n/s	n/s	n/s
Simpson, R. J., et al. (2014)	yes	Definite MS	Clinician recording	None Specified	2766 females/ 1060 males. av. 53.4 years	yes	yes	no	Consecutive
Smith, S. J. & Young, C. A. (2000)	no	Definite MS	HADS	BDI, MRS, two visual analogue scales.	61 females /88 males av. 46 years	yes	yes	no	Consecutive
Spain, L. A., et al. (2007)	yes	Definite MS (Posars criteria)- 54% MSRR, 30% MSSP, 10% MSPP, 6% intermediate subtype.	HADS	EDSS, SDMT, IPQ, SF-36	458 females/ 122 males. av. 46.7 years	yes	yes	no	Convenience
Stenager, E., et al. (1994)	no	Definite MS (Posars criteria)	STAI	EDSS, measures of cognitive impairment.	52 females /42 males av. 42. 6 years	yes	yes	no	n/s
Suh, Y., et al. (2010)	yes	Definite MS	HADS	PDDS	62 females/ 34 males av. 48.6 years	yes	yes	no	Convenience
Szilasiova, J., et al. (2011)	no	Definite MS- 77.2% MSRR, 18.4% MSSP, 4.4% MSPP	HADS	FSS, SF-36, EDSS	82 females/ 32 males. av. 36.1 years	yes	yes	no	Consecutive
Tadic, D. & Dajic, V. (2013)	no	Definite MS (McDonald	HAM-A	EDSS, MSQoL-54, HDRS	28 females/ 22 males.	yes	yes	no	n/s

		Criteria)			av. 41.2 years			
Tan-Kristanto et al (2015)	Yes	Definite MS (McDonald criteria)	DASS	EDSS, RSA, MSSE, Brief COPE	117 women, 12 men av=38.41 years	Yes	No	convenience
Theaudin et al (2016)	Yes	Definite MS (Posar and McDonald criteria)	HADS	EDSS	489 females/ 222 males av. 44.8 years	yes	no	consecutive
Thornton, E. W., et al. (2006)	no	Definite MS	HADS	WQMS, PSQW, SESMS	27 females / 12 males av. 48.3 years	yes	no	Randomised
Tsivgoulis, G., et al. (2007)	yes	RRMS	STAI	BDI, EDSS	56 females/ 30 males. av. 39 years	yes	no	Consecutive
Uca et al (2016)	No	RRMS (McDonald criteria)	SCID-I/CV	EDSS, SCID-II/CV	96 females, 15 males av. 35.1 years	yes	no	n/s
Uguz, F., et al. (2008)	no	RRMS (42 in exacerbation phase, 32 in remission phase)	DSM	EDSS	50 females/ 24 males av. 34.57 years	yes	no	Consecutive
Van Der Hiele, K., et al. (2014)	yes	RRMS patients	HADS	SF-36, BADS DEX, FIS	39 females / 5 males. av. 37.2 years	yes	no	Consecutive
Van Der Hiele, K., et al. (2010)	yes	Benign, MSRR, MSSP, MSPP	HADS	BADS-DEX, SCWT, WCST, EDSS	n/s	no	n/s	n/s
Van der Hiele, K., et al. (2012)	yes	Benign, MSRR, MSSP, MSPP	HADS	SF-36, FIS, EPCL	392 females/ 138 males. av. 48.3 years	yes	no	Convenience
Van der Hiele, K., et al. (2012)	yes	Benign, MSRR, MSSP, MSPP	HADS	BADS, EPCL, UCL, BAD DEX, cognitive and neuropsych assessments	86 females/ 28 males av. 50.2 years	yes	no	Convenience
Visser, L. H., et al. (2009)	n/s	Definite MS	HADS	BADS-DEX, DIP, CERQ, FIS, AMS, UCL, SCL-R-90	n/s	no	n/s	n/s
Voiticovschi-Iosob, C. & Moldovanu, I. (2013)	n/s	Definite MS	STAI	BDI, SF-36, Structured pain questionnaire	n/s	no	n/s	n/s
Vuger-Kovacic, D., et al. (2007)	no	Definite MS	CCEI	Locus of control Inventory	n/s	yes	yes	no	n/s
Weisbrot, D., et al. (2012)	n/s	Definite MS	K-SADS	PedsQL, CGAS	29 females/ 16 males.	no	n/s	n/s	n/s

					av. 15.7 years				
White, C. P., et al. (2008)	yes	Definite MS 66% RRMS, 12% PPMS, 9% SPMS, 13% unsure of type	MHI	MFIS, MHI	75 females/ 26 males. av. 50 years	yes	yes	no	Randomised
Ziegler, K., et al. (2010)	n/s	Definite MS	DSM-IV	CAR	n/s	no	n/s	n/s	n/s
Zorzon, M., et al. (2001)	no	Definite MS	HADS	DSM	62 females / 33 males av. 39.5 years	yes	yes	no	Consecutive

Table 2: Prospective Studies

Authors, Year	Multi-Centre	Type of MS	Measure of anxiety	Other measures used	Gender/Age	Full paper	Eligibility Criteria Specified	Powered	Recruitment strategy
Bianchi, V., et al. (2014)	no	RRMS	HAM-A	WCQ, HAM-D	30 females / 9 males av. 28.8 years	yes	yes	no	Consecutive
Brown, R. F., et al. (2009)	yes	Definite MS	STAI	EDSS, SEFCI, LEDS, FIS, BDI, WOCQ, LOT, MHLC, SSQ, PSQI	81 females / 101 males av. 42.6 years	yes	yes	no	n/s
Burns, M. N., et al. (2013)	yes	MSRR, MSSP	HADS	CES-D, MINI	82 females/ 17 males. av. 42.7 years	yes	yes	no	Randomised
Christodoulou, C., et al. (2009)	yes	28 MSRR, 10 MSSP	STAI	CESD, CMDI, PANAS, FSS, AES, MS cognitive batteries, EDSS	22 females/ 16 males. av. 45.5 years	yes	yes	no	n/s
Dalos, N. P., et al. (1983)	no	Definite MS	GHQ-28	None	66 females / 34 males av. 40.4 years	yes	yes	no	Consecutive
Diaz-Olavarrieta, C., et al. (1999)	no	RRMS and Chronic Progressive	NPI	EDSS, MMSE	30 females / 14 males av. 33 years	yes	yes	no	Convenience
Giordano, A., et al. (2011)	yes	Definite MS	HADS	EDSS	56 females/ 26 males. av. 35.2 years	yes	yes	no	Randomised
Hartoonian et al (2015)	yes	Self-reported diagnosis	HADS-A	EDSS, NRS, FSS,	421 females, 92 males	Yes	Yes	No	convenience

		MS		PHQ-9	Av. 51 years				
Hoang et al (2016)	Yes	Definite MS	ICD-10 diagnosis	None	n/s	Yes	Yes	No	Consecutive
Janssens, A., et al. (2006)	yes	Recently Diagnosed	HADS	IES, EDSS	71 females/ 30 males. av. 37.5 years	yes	yes	no	Consecutive
Johnson, K., et al. (2012)	yes	Definite MS	PROMIS	Neuro-QoL	n/s	no	n/s	n/s	n/s
McCabe, M. P. (2005)	yes	Definite MS	POMS	WHOGOL-100, WOCQ	163 females / 80 males av. 44.86 years	yes	yes	no	Randomised
McKay et al (2016)	Yes	Definite MS	HADS	CAGE, EDSS	714females /235 males Av. 48.6 years	Yes	Yes	No	consecutive
Olivares, T., et al. (2012)	n/s	Definite MS	HADS	BRB, MSNQ-S, FFS, MS-QOL	40 females/ 10 males av. 36.8 years	no	n/s	n/s	n/s
Pakenham, K. I. & Samios, C. (2013)	yes	Definite MS	DASS-21	AAQ, MAAS	54 females / 15 males av. 42.12 years	yes	yes	no	Randomised
Pekmezovic, T., et al. (2012)	n/s	Definite MS	HAM-A	HDRS, MSQoL, EDSS	n/s	no	n/s	n/s	n/s
Potagas, C., et al. (2008)	no	Definite MS	HAM-A	SRRS	37 females. av. 32.8 years	yes	yes	no	n/s
Solari, A., et al. (2010)	n/s	92% RRMS	HADS	EDSS	56 females/ 26 males av. 35 years	no	n/s	n/s	n/s
Wood, B., et al. (2013)	yes	Definite MS (McDonald criteria)	HADS	FSS, EDSS, MSSS	125 females/ 73 males. av. 48.2 years	yes	yes	no	Consecutive

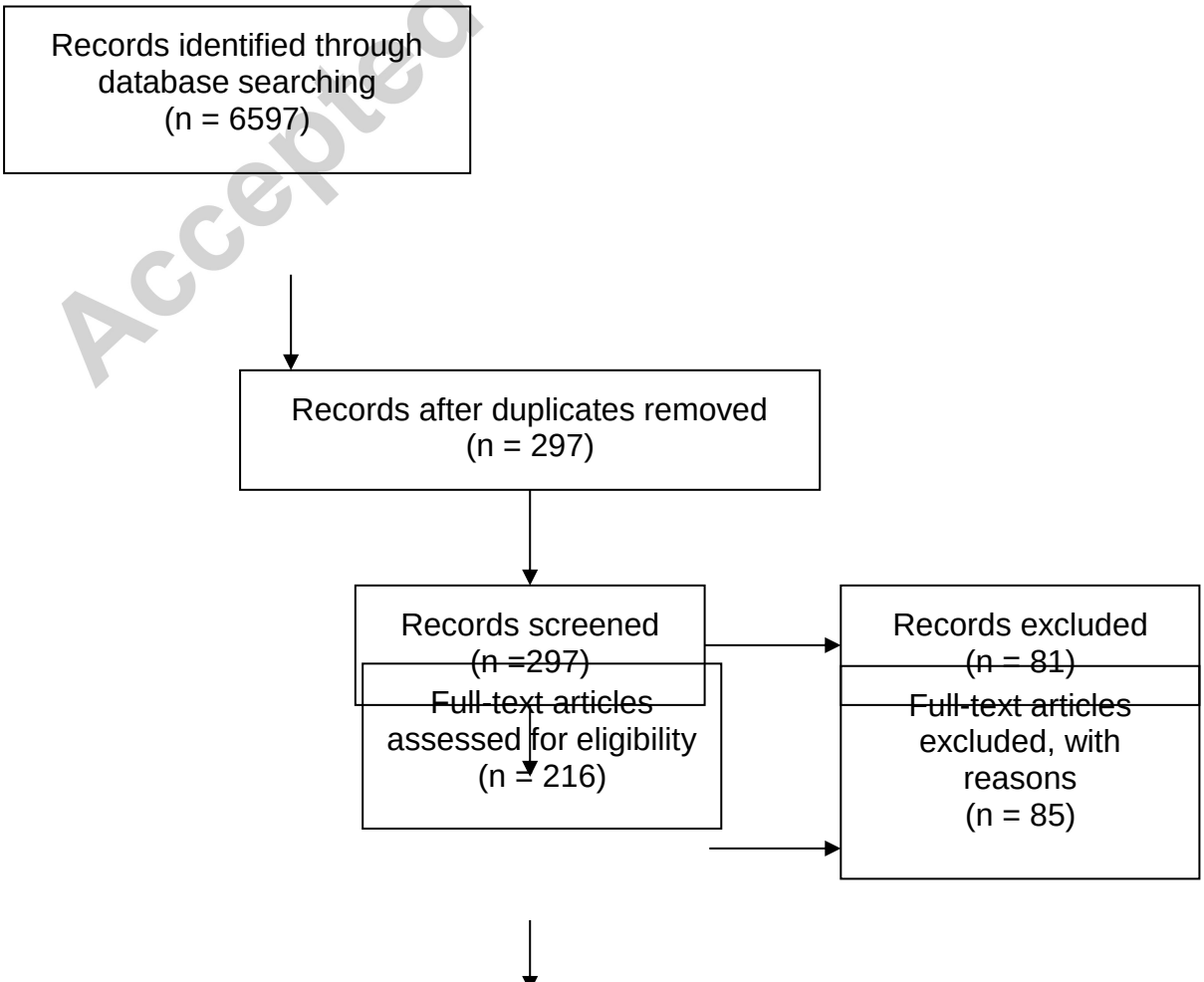
A box-score method was used to quantify the relationships between the factors associated with anxiety among PwMS (Matcham, Alib, Hotopf, & Chalder, 2015). The method involved tabulating each factor and its relationship with anxiety, in terms of significance and direction: a positive sign (+) was given for a positive significant association between variables: a negative sign (-) for a negative significant association between variables and a naught (0) for no association between variables (Green & Hall, 1984). This table (see Table 3) also included study design (cross-sectional or prospective) and level of analysis (bivariate or multivariate). Thus tabulated associations could be synthesized alongside indicators of study quality. Data from all studies were included in the box-score table except those that focused

uniquely on prevalence rates and those that focused on subtypes of anxiety such as OCD, Social Anxiety or PTSD. These excluded studies will be outlined in detail below. Data from both bivariate and multivariate models were included in order to retain as much data for comparison as possible.

3. RESULTS

3. 1. Overview

The literature search yielded 6494 relevant articles (Figure 1). Removal of duplicates and screening of titles and abstracts left 216 articles for full-text screening. Full versions of these articles were obtained and reviewed against inclusion criteria. Eighty-five of these did not meet the eligibility criteria. The most common reason for exclusion was not having measured or reported anxiety. One hundred and thirty-one studies were deemed eligible for inclusion in the narrative synthesis. Fifty-two percent of the studies used the Hospital Anxiety and Depression Scale (HADS). In the remaining studies, 20 other previously validated questionnaires were used or anxiety was measured by assessment with a clinician (see Appendix B).



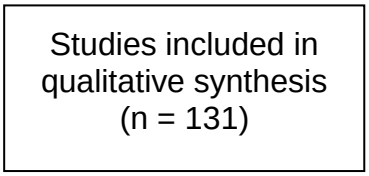


Figure 1 PRISMA flow diagram

The sample size of studies (N=131) ranged from 19 to 5084 participants. However, the majority of studies had sample sizes of between 50 and 200 participants. Most of the studies in the review included both men and women. However, within these studies women represented the majority of participants. Three studies only included women. Although not all studies reported the age of participants, in those that did, the average range was between 15.7 years and 50.9 years. Most studies focused on prevalence rates, cognitive processes, physical, social or psychological factors. An overview of all study characteristics for both cross-sectional (N=112) and prospective studies (N=19) was carried out (see Appendix C). Data were typically analysed using correlations or regression.

Table 3: Box Analysis of Factors Associated with Anxiety for PwMS

Category	Factor	CS Bivariate	CS Multivariate	PS Bivariate	PS Multivariate
Demographics	Gender (female)	++++++++00	+	+0	++0
	Age (younger)	++++++	++	0	+
Cognitive	Dysfunction	++++00	+++++000		+
	Cognitive change				+
	Perception of cognitive dysfunction	+++	+		
	Self-reported memory problems		0		
	Illness intrusiveness		+		
	Illness representation (Illness identity, cyclical timeline and illness coherence)	0	+		
	Perception of risk		+		
	Neuropsychological functioning	00	0		+
Mood Related	Depression	++++++++++	++++++++	+	++++++
	Suicidal thoughts	+			
	Alexithymia	+			
	Low Self-efficacy	+	++		
	Low emotional well-being	+			
	Low general well-being	+			
	Psychological Distress		+		
	Difficulty managing mood		+		
	Worry	+			
	Stress	++	+++		
	Health worry/anxiety		++0		

Personality	Extroversion	+			
	Neuroticism	+	+		
	Conscientiousness		+		
	Low optimism				+
	Personality disorder (SCID-II)		+		
Coping	Avoidance coping		++		0
	Accepting Responsibilities				+-
	Mindfulness				+
	Resilience		-		
	Distress disclosure		+		
	Planning		+		
	Positive interpretation		-		
	Use of social support	-	-		-
	Emotion focused coping	++	+++		0
	Problem focused coping	-			0
	No relaxation training				+
	Unhealthy behaviours (eg. drinking to excess, smoking)	+			++
Physical functioning	Sleep disturbances	0+	++		
	Better health status		+-(Young)		
	Long Duration	+00000--	00--	0	+
	Wheelchair bound		-		0
	Level of disability	++++++++++00-00	++++++++++0	00	0
	Daily functioning	-	+		
	Physical activity		0		
Symptoms	Number of symptoms	+			
	Pain	++++0	++		
	Fatigue	++++0	+++0	++	
	Exacerbations/course of illness	000	++0	++	+
	Dyspepsia	+			
	Spasticity	+			
	Speech difficulties	+			
Biological	Other physical health problem	+(Epilepsy)			
	Frontotemporal changes			0	
	Lesion loads	0			
	Brain Volume	0			
Medical	Poor Adherence of medication	+			
	Immunotherapy status				+
	Treatment with disease modifying drug (DMD)				+
	Number of hospitalisations		+		
Social Factors	Lack of Education	+-	0		
	Negative life events	+			+
	Problems in family life	+			
	Few MS group activities		+		
	Lack of information on MS		+		
	Unemployment	0	++++		-
	Quality of life	+++	+++++	++	
	Presenteeism at work	+			
	Lower social activity/support	+	0	+	
Type MS	Relapsing Remitting Multiple Sclerosis (RRMS)	0++(Women)	+		
	Secondary Progressive Multiple Sclerosis (SPMS)	++			

+ Positive association with anxiety ($p<0.05$); - negative association with anxiety ($p>0.05$); 0 no association with anxiety; CS (Cross-Sectional Study); PS (Prospective Study)

Elements of study quality were also examined by applying a previously used quality-assessment tool which was appropriate for both cross-sectional and prospective study designs (Matcham, Rayner, Steer, & Hotopf, 2013) (see Table 4). The tool was adjusted slightly and included: whether a full paper was available rather than just an abstract; whether anxiety was measured using a validated tool; whether the recruitment strategy was randomised or consecutive; whether the participants were recruited from multiple centres; whether there was a control group; whether eligibility criteria were specified and whether the study was adequately powered. In the case where studies did not report anything for a particular eligibility indicator, they were allocated to the no category.

Table 4: Quality Assessment of Studies including Conference Abstracts

Study Type	Full paper available	Validated measure of anxiety	Randomised/consecutive recruitment strategy	Multi-centre	Control Group	Eligibility criteria specified	Adequately powered
Cross Sectional-studies	69.57%	94.78%	32.76%	39.13%	14.81%	65.21%	0.93%
Prospective studies	78.95%	100%	52.63%	63.15%	47.47%	78.95%	0%

The remainder of the results section summarises and synthesizes findings regarding the factors associated with anxiety (grouped into thematically or conceptually related categories). Given the large number of studies reviewed, thorough discussion of individual studies is beyond the scope of this report. The focus is therefore on providing a broad overview of the evidence available, including the conceptual backgrounds of the research. The strength of associations are later outlined (see Appendices C). The results are considered under the following sections: Prevalence of Anxiety and Subtypes; Demographics; Cognition; Physical Functioning; Mood Related Factors; Personality; Social Factors and Coping.

3. 2. Prevalence of Anxiety and Subtypes

Fifty-two cross-sectional and six prospective studies in the review included prevalence rates. Although rates for anxiety tended to differ across studies, all

studies reported higher rates of anxiety among PwMS in comparison to control groups when present. The prevalence of anxiety generally ranged between 4% and 57% (Montel et al, 2007; Garfield et al, 2012). In a prospective study, the prevalence of anxiety was 25.4% at baseline, however, this decreased over time after diagnosis (Wood et al, 2013).

Other studies examined prevalence rates of anxiety and anxiety subtypes for PwMS; 11.8% was reported for GAD, 1.2% for panic disorder, 7.1% for specific phobias and 11.8% for OCD (Shabani et al, 2007). Another study reported 18.9% for GAD, 18.9% for specific phobia and 14.9% for OCD (Uguz et al, 2008). Furthermore, the same study found that OCD was significantly more common among patients experiencing a relapse compared to patients in the remission phase (Uguz et al, 2008). Similar to the previously mentioned studies, a prevalence rate of 16.1% for OCD was also reported (Foroughipour et al, 2012). In this study, OCD was significantly correlated with a higher level of disability and long duration of disease. Furthermore, biological factors such as cranial, cerebellar, autonomic, sensory and motor nerve involvement were also associated with OCD (Foroughipour et al, 2012).

A prevalence rate of 16% was reported for PTSD in PwMS (Chalfant et al, 2004). Higher level of disability and having another health condition were both significantly related to these symptoms (Counsell et al, 2013). Furthermore, a prevalence rate of 24% was reported for PTSD that was associated with MS diagnosis. These patients showed significantly lower self-efficacy and social support (Ziegler et al, 2010). Level of education, GAD and depression were also reported as significant determinants of PTSD (Ostacoli et al, 2013).

Two studies that specifically focused on clinically significant social anxiety reported prevalence rates of 29.8% and 30.6% respectively for PwMS (Podor et al, 2014; Podor et al, 2009). Half of these patients with social anxiety had GAD and a quarter had depression. Severity of social anxiety symptoms was associated with reduced health-related quality of life and was not related to neurological disability.

3. 3. Demographics

The eleven cross-sectional and six prospective studies that focused on gender differences associated with anxiety varied. Many studies found females were significantly more anxious than males at bivariate level (Dahl et al, 2009; Feinstein et al, 1999; Da Silva et al, 2011) and multivariate level (Theaudin et al, 2016; Wood et al, 2013; Chalk, 2007; Solari et al, 2010). Similarly, it was found that being female was an independent predictor of anxiety at multivariate level (Giordano et al, 2011). However, other bivariate studies found no gender differences for those who reported high levels of anxiety (Anhoque et al, 2011; Diaz-Olavarrieta, 1999; Hakim et al, 2000; Paredes et al, 2012). One study found slightly higher anxiety levels amongst men (31.1%) in comparison to women with MS (29.7%) (Dahl et al, 2012).

Seven cross-sectional and two prospective studies in this review investigated the relationship between anxiety and age. Many studies found younger age was associated with anxiety symptoms (Wood et al, 2013; Hakim et al, 2000; Beiske et al, 2008; Leonavicius et al, 2013). However, three studies found no evidence for increased levels of anxiety among younger PwMS (Diaz-Olavarrieta et al, 1999; Espinola-Nadurille et al, 2010; Harding et al, 2012).

3. 4. Cognition

Many studies found that cognitive dysfunction (deficits in thinking, remembering, and reasoning) was significantly correlated with increased anxiety (Farrell et al, 2011; Akbar et al, 2011; Bamer et al, 2008; Bruce et al, 2009; Visser et al, 2009). Anxiety was also negatively correlated with self-awareness of cognitive dysfunction (Grech et al, 2015; Van der Hiele et al, 2010; Van der Hiele et al, 2012). Although, self-reported memory problems did not predict anxiety (Bruce et al, 2010), anxiety was found to independently predict cognitive performance (Julian et al, 2009). Another study found that anxiety predicted perceptions of global cognitive functioning but not objective cognitive performance (Middleton et al, 2006). A prospective study found that anxiety was a significant predictor of cognitive change over time (Christodoulou et al, 2009). Despite these findings, other studies found no

association between anxiety and cognitive dysfunction (Middleton et al, 2006; Goretti et al, 2014; Kostaras et al, 2008). Furthermore, anxiety was found to have no association with perception of disability (Smith et al, 2000). However, others found patients' illness representations were a significant predictor of anxiety (Jopson et al, 2003) and higher perception of two-year risk of wheelchair dependence was significantly related with high levels of anxiety (Janssens et al, 2004).

Neuropsychological performance, which examines cognitive, motor, behavioural, linguistic, and executive functioning, failed to reveal significant correlations with anxiety in both cross-sectional and prospective studies (Bruce et al, 2009; Maia et al, 2011; Olivares et al, 2012).

3. 5. Physical Functioning

Twenty-eight studies investigated the association between level of disability and anxiety symptoms; eighteen of these reported a significant relationship between high level of disability and high level of anxiety at either bivariate or multivariate level (Tan-Kristanto et al, 2015; Anhoque et al, 2011; Askari et al, 2014; Curral et al, 2011; Ionescu et al, 2012, Sarisoy et al, 2013). Multiple linear regression analysis showed that depression and disability level were independent predictors of anxiety (Askari et al, 2014). A strong correlation was found between the number of symptoms inherent to the disease and anxiety (Roy-Bellina et al, 2010). Bogart (2015) also reported that disability identity; affirming one's status as a person with a disability, was a predictor of lower anxiety among PwMS.

Symptoms and disease related factors

In total, fourteen studies investigated the relationship between duration of illness and anxiety and in general findings were inconsistent. However, a recent study with a cohort of 5084 MS patients found that PwMS have an increased risk of anxiety during both the pre-diagnostic and post-diagnostic period compared to controls (Hoang et al, 2016). Furthermore, a prospective study with 513 PwMS reported that anxiety at time one predicted anxiety four

months later while controlling for demographic and disease related variables (Hartoonian et al, 2015).

The seven studies that investigated the relationship between pain and anxiety found a significant relationship between high levels of pain and anxiety at bivariate and multivariate level, with the exception of one cross-sectional bivariate study. Similarly, ten studies examined the relationship between anxiety and fatigue; all of these reported significant results either at bivariate or multivariate levels with the exception of two cross-sectional studies. Four studies examined the relationship between sleep disturbance and anxiety. Two multivariate studies and one bivariate study found strong correlations (Bamer et al, 2008; Leonavicius et al, 2014). However, one bivariate study found no association between anxiety and sleep disturbance (Bruce et al, 2009).

Eight studies examined the relationship between course of illness or relapses and anxiety. The four prospective studies showed that number of relapses over time could significantly increase anxiety levels (Brown et al, 2009; Dalos et al, 1983; McCabe, 2005; Potagos et al, 2008).

A range of biological factors was investigated in relation to anxiety. Anxiety did not correlate significantly with any of the measures of regional and total lesion loads and brain volume (Zorzon et al, 2002). Similarly, anxiety had no significant association with frontotemporal changes measured by MRI (Diaz-Olavarrieta, 1999).

Medical Factors and treatment

Adherence is often a key issue for those who are chronically ill. One study reported a significant relationship between high level of anxiety and low level of adherence at bivariate level (Sidorenko et al, 2010). Anxiety levels were also significantly associated with lower levels of social support (Reade et al, 2012). Knowledge of disease information was found to improve anxiety levels (Niino et al, 2012).

3. 6. Mood Related factors

Overall, nineteen cross-sectional and eight prospective studies investigated the relationship between anxiety and depression. Strong positive correlations were consistently found between anxiety and depression in the cross-sectional studies (Dahl et al, 2009; Smith et al, 2000; Aloulou et al, 2011; Garfield et al, 2012; Anhoque et al, 2011; Espinola-Nadurille et al, 2010; Arnett et al, 2011; Karadayi et al, 2014; Leonavicius et al, 2011; White et al, 2008). Furthermore, multiple linear regression analysis showed that depression was an independent predictor of anxiety in patients (Giordano et al, 2011; Anhoque et al, 2011; Bamer et al, 2008). Prospective studies have further shown a strong association between depression and anxiety (Solari et al, 2010; Brown et al, 2009; Pakenham et al, 2013).

3. 7. Personality

Both extroversion and neuroticism were strongly correlated with anxiety symptoms among PwMS (Liu et al, 2009). Furthermore, anxiety accounted for unique variance in conscientiousness (R^2=.23, F=25.37, P<.001) and neuroticism (R^2=.65, F=153.09, P<.001) at the multivariate level (Bruce et al, 2011). A prospective study found anxiety was strongly correlated to low dispositional optimism at baseline (Brown et al, 2009). Recently, a study also found that PwMS and a personality disorder had a significantly higher frequency of any anxiety disorder including PTSD (Uca et al, 2016).

3. 8. Social factors

Seven studies focused on the role anxiety had on employment and job productivity. Presenteeism, the act of attending work when sick, was significantly associated with elevated levels of anxiety (Glanz et al, 2012). Changes in employment status after MS onset, also had a negative impact on anxiety levels at multivariate but not bivariate level (Kikuchi et al, 2013; Niino et al, 2012). Patients without anxiety were significantly more likely to be employed (Tan-Kristanto et al, 2015; Krokavcova et al, 2010). However, one

study found no relationship between employment and anxiety (Van der Hiele et al, 2014).

Significant associations were found between anxiety and negative life events, problems in family life and social functioning (Potagas et al 2008; Liu et al, 2009). Mixed results were found for the relationship between anxiety and level of education as both low level of education and having a university education were significantly associated with high levels of anxiety (Shabani et al, 2007; Da Silva et al, 2011). Quality of life (QoL) was examined in eight cross-sectional and two prospective studies. Anxiety was strongly associated with lower QoL (Dubayova et al, 2012; Fisk et al, 2014l Fruhwald et al, 2001; Szilasiova et al, 2011; Tadic et al, 2013; Spain et al, 2007; Olivares et al, 2012; Pekmezovic et al, 2012), at all levels of illness severity (Ionescu et al, 2012).

3. 9. Coping

High levels of anxiety were consistently associated with emotional preoccupation coping (focusing on the emotional consequences of MS) (Tan-Kristanto et al, 2015; Roy-Bellina et al, 2010; Kehler et al, 2009; Montel et al, 2007; Roy-Bellina et al, 2009), avoidance coping (denial) (Tan-Kristanto et al, 2015), drinking to excess (Dahl et al, 2009) and substance abuse (Milanlioglu et al, 2013). A recent, large, representative study found alcohol dependence and smoking were associated with anxiety (McKay et al, 2016). Prospective studies found that smoking and no previous training in relaxation exercises were predictors of anxiety (Brown et al, 2009). Somewhat surprisingly planning, acceptance and focus on emotional ventilation worsened symptoms (Brajkovic et al, 2009).

Research examining predictors of anxiety found positive reinterpretation, social emotional support and humour predicted an improvement of anxiety symptoms. “Problem focused coping” (targeted at reducing the stressor) was also negatively correlated with anxiety (Roy-Bellina et al, 2009). A prospective study found that patients who accessed social support to cope had a reduction in anxiety scores in contrast to the population norm (Johnson et al,

2012). Anxiety was also significantly associated with low levels of acceptance and mindfulness (Pakenham et al, 2013).

4.DISCUSSION

4. 1. Summary of main findings

The results of this review suggest that anxiety is associated with a variety of physical, psychological, cognitive and social factors, some of which are amenable to change, as highlighted in table 3. Overall, the high prevalence of anxiety that was reported across majority of the studies for PwMS contrasted strongly to a prevalence rate for anxiety of 5.1% for the general population (Aarsland & Figved, 2007). Many studies found significant associations between high levels of anxiety and depression in PwMS. In one study, depression was found to be the most significant factor associated with anxiety (Garfield et al, 2012). The significance of other factors such as self-efficacy, level of disability and stress were diluted due to their influence in multivariate analysis. Although prospective studies were limited in number, one prospective study carried out over two years revealed that depression strongly predicted anxiety, and anxiety strongly predicted later depression (Brown et al, 2009). In many of the studies women represented the majority of participants. This gender imbalance is likely due to the higher prevalence of MS among women. It has been suggested that a gender ratio approaching 4:1 exists which is similar to other autoimmune diseases such as rheumatoid arthritis (Orton et al., 2006).

Anxiety and depression were predicted by a combination of unhealthy lifestyle behaviours (e.g. drug use, smoking) (Brown et al, 2009; McKay et al, 2016). Several studies suggested that various other types of coping strategies were linked to anxiety symptoms. PwMS were less likely to use positive and problem-focused strategies in comparison with the general population, and used avoidance and emotional preoccupation strategies more frequently (Goretti et al., 2009).

Although low level of social support was associated with higher level of anxiety it is important to acknowledge the complex nature of social support in relation to health (Matcham et al., 2015): those with anxiety may have distorted perceptions of the availability of social support. Furthermore, personality factors such as neuroticism may confound associations between social support and health, and there are genuine cultural differences in perceptions of “adequate” social support (Thoits, 2011).

4. 3. Methodological critique of reviewed studies

Overall, despite the large number of studies relevant to this review, the quality of the research was disappointing. In some cases, the strengths of associations between anxiety-related factors were not reported, for example when only the abstract of the study was available.

The fundamental limitation of the reviewed research was that most studies (112 out of 131) were cross-sectional; without prospective evidence causal relationships cannot be established. Nevertheless, understanding the factors associated with anxiety provides an insight into issues that could be tackled through psychological interventions, leading to better outcomes.

Another problem was that some studies used small sample sizes and were therefore underpowered to detect relationships, or prevents the application of positive findings to larger populations (Kothari, 2004). Inadequate reporting of participant characteristics made it difficult to interpret study findings or make assumptions about generalisability. Some studies failed to report important demographic data or recruitment strategies which prevented the reporting of descriptive statistics for demographic data and information for quality assessment.

Other significant weaknesses were linked to the measurement of anxiety and factors associated with anxiety. The studies relied primarily on participant self-report measures. This may mean that results were influenced by shared-

method variance which could threaten the validity of conclusions made regarding the relationships between measures (Huang, Liao, & Chang, 1998). In some studies a rating scale for anxiety was included alongside many other psychometric measures, therefore formal Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) diagnoses could not be made. The use of scales can cause difficulty with interpreting data and making accurate assumptions. Screening tools for anxiety disorders in comparison to depression can be particularly problematic because different kinds of anxiety disorders generally have more heterogeneous symptoms than different types of depressive disorders. In addition to this, normal expressions of anxiety in clinical samples generally exhibit a greater overlap with anxiety symptoms shown by patients that are diagnosed with an anxiety disorder (Rose & Devine, 2014). It is important to consider that in some studies anxiety was not the primary focus of research and therefore it was difficult to interpret findings. However, we felt that it was important to include these studies to ensure this paper gave a comprehensive overview of the literature to date.

Some studies also failed to report results in conventional formats (e.g. a regression analysis table including beta coefficients and p-values (American Psychological Association, 2009). This prevented the interpretation of results about the relative importance of factors associated with anxiety.

4. 4. Models of understanding anxiety in the context of MS

A number of theoretical models of anxiety have previously been proposed, including the Avoidance Model of Worry and GAD (Borkovec, 1994), the Intolerance of Uncertainty Model (Dugas, Letarte, Rheaume, Freeston, & Ladouceur, 1995), the Metacognitive Model (Wells, 1995), the Emotion Dysregulation Model (Mennin, Heimberg, Turk, & Fresco, 2002) and the Acceptance-based Model of GAD (Roemer & Orsillo, 2002). These offer valuable insights into the basic nature of GAD and the necessary steps for successful treatment (Behar, DiMarco, Hekler, Mohlman, & Staples, 2009). They share a common emphasis on the central importance of avoidance of

internal experiences. However, given their general nature they do not specifically account for the unique worries associated with MS. The Working Model of Adjustment to Multiple Sclerosis (Dennison, Moss-Morris, & Chalder, 2009) has been proposed as a provisional working model of adjustment to MS that incorporates many specific concerns associated with MS. Beck's model of emotional disorders (Beck, 2011) can usefully be applied to people with anxiety in the context of MS (see figure 2). The model assumes that anxiety can be triggered by critical events. These events may include developing the disease, fear of disability or other life stressor. Subsequently, avoidance coping, low mood or stress and unhelpful thinking maintains the symptoms.

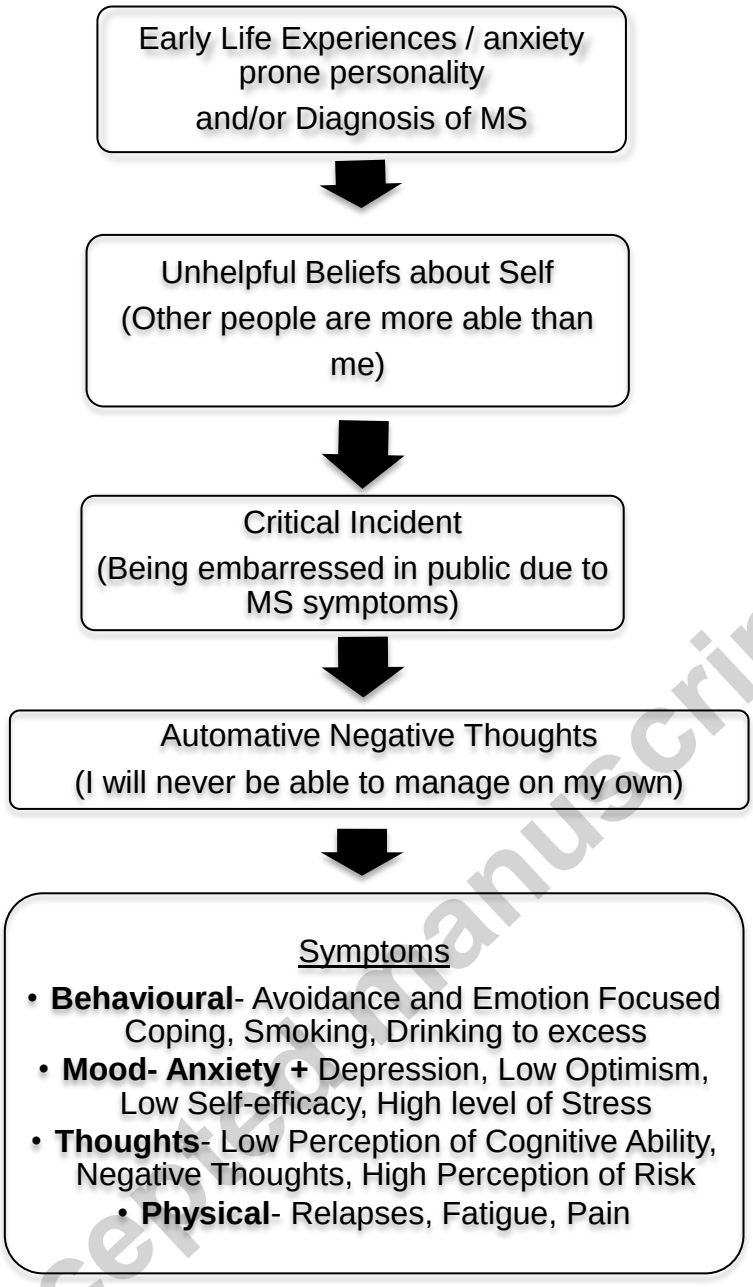


Figure 2: A Working Conceptual Model of Anxiety for PwMS

4. 2. Clinical implications of key findings

The findings of this review have many clinical implications. Firstly, although anxiety is commonly reported in PwMS, it is often not treated (Beiske et al, 2008). It is unknown whether this is due to the failure of clinicians to diagnose mental health problems or whether PwMS decline treatment. We think the

latter unlikely. Nonetheless, this review suggests the importance of detecting and treating anxiety when patients are first diagnosed with MS. They should then be monitored throughout the course of the illness.

Few studies to date have specifically targeted anxiety within an MS population. It is difficult to know why this is the case but it may be that the more overt physical consequences of MS have been prioritized or it may be due to an over-focus on depression and cognition. One small study of individual cognitive behavioural therapy versus psychotherapy found a reduction in anxiety levels in people who received CBT (Foley, Bedell, LaRocca, Scheinberg, & Reznikoff, 1987). Similarly, a small study of guided imagery and relaxation found reduced anxiety scores in PwMS (Maguire, 1996).

Comorbid anxiety and depression can have important consequences for patients in terms of their MS, their ability to engage in treatment and their quality of life (Garfield et al, 2012). Although interventions targeted at comorbid depression and anxiety have been neglected within the MS literature, treatments such as trans-diagnostic interventions that use the same underlying treatment principles across mental disorders, have been beneficial for general adult populations with comorbid anxiety and depression (McEvoy, Nathan, & Norton, 2009). These interventions apply core CBT-based treatment principles and techniques such as graded exposure and cognitive restructuring which target the common processes underlying anxiety and depression, rather than targeting the symptoms of specific disorders. Furthermore, a systematic review of existing literature on these types of treatments for depression and anxiety disorders in adults found large and significant reductions in both anxiety and depression, and moderate improvements in quality of life (Newby, McKinnon, Kuyken, Gilbody, & Dalgleish, 2015). Previous research indicates that PwMS benefit from strategies that enhance self-efficacy, a transdiagnostic process (Fraser & Polito, 2007) (Nodhturft et al., 2000). Future research should therefore investigate the efficacy of psychological interventions for PwMS.

Pharmacologically serotonin reuptake inhibitors are considered first-line treatment in depression comorbid with a spectrum of anxiety disorders (Coplan, Aaronson, Panthangi, & Kim, 2015). It has further been recommended that combining benzodiazepines with an SSRI can lead to more rapid control of anxiety and improved control of episodic or situational anxiety (Dunlop & Davis, 2008). There is little evidence to date on the pharmacological treatment of depression and anxiety specifically for PwMS. A Cochrane review on pharmacologic treatment of depression for PwMS reported only two randomised controlled trials, which both had significant problems within their methodology including loss of follow-up data (M.W. Koch, Glazenborg, Uyttenboogaart, Mostert, & De Keyser, 2011) A recent review indicated high antidepressant use among PwMS and suggested that these drugs are possibly helpful in idiopathic major depressive disorder or based on patient and doctor beliefs that they are beneficial (M. W. Koch et al., 2015). Overall, it appears that large, well-controlled trials are required for pharmacological treatments in MS in order to establish a firm evidence base on their efficacy for both depression and anxiety.

4. 5. Limitations of the review

A number of limitations of this review should be considered. Firstly, due to the large number of studies available, only studies published in peer-reviewed journals were considered. It was beyond the scope of the review to examine unpublished studies and the “grey literature”. Unfortunately this decision may result in bias since unpublished studies are more likely to demonstrate no relationships.

Secondly, due to the large number of studies, the review included only quantitative research (including one mixed methods study); qualitative studies were excluded. Although qualitative research does not generally determine whether one variable can influence another or conclusively establish relationships, qualitative research can offer rich and detailed understandings on the complex associations of interest.

Finally, there has been no previous systematic review conducted to date on anxiety among PwMS. In this study, because the inclusion criteria were broad, the studies were vastly heterogeneous, and so not conducive to an overall synthesis. Furthermore, the broad inclusion criteria resulted in studies that had weak methodology and did not provide strong evidence of associations, particularly causal relationships. This review aimed to draw attention to the dearth of high quality evidence, improve the quality of future research and highlight areas in which future studies should focus on.

4. 6. Suggestions for future research

Specifically, prospective studies are needed to determine which factors precede or predict anxiety. Ideally, studies need to employ prospective designs and assess large samples of participants when MS is first diagnosed and thereafter. It is important that recruitment strategies are specified and power calculations are stated to improve the overall quality of this literature.

Future studies should also examine the neuroimaging correlated of anxiety as has been done previously researched for depression and cognition in MS (e.g.(Malkki, 2015; Mrabet, Ben Ali, Kchaou, & Belal, 2014). This may enhance our understanding of how potential biomarkers such as structural brain changes relate to anxiety in PwMS.

5. CONCLUSION

This review has shown that high levels of anxiety exist among PwMS, highlighting the need for early intervention and treatment of anxiety throughout the course of MS. Anxiety in MS is associated with a number of physical, cognitive, social and psychological factors which have been conceptualized in a model of anxiety. Due to the high levels of comorbidity with depression, many PwMS are likely to benefit from psychological and pharmacological interventions targeting both anxiety and depression.

Conflict of interest/Role of Funding Source

TC receives salary support from the National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed in this article are those of the authors and not necessarily those of the NIHR or the NHS. EB and FM declare that they have no conflicts of interest.

Appendix A: Search terms

A search was conducted for articles published between January 1980 and September 2016 which examined MS-related anxiety. Search terms were customized to each database and combined with key word searches e.g. "anxiety", "anxiety disorder", "anxious" and terms such as "Multiple Sclerosis", "MS", "determine*", "predict*", "correlate*", "relationship*", "prevalence", "intervention*", "association*" and "outcome*".

Appendix B. Anxiety Measures used in studies (N=122)

Anxiety Measure	Number of Studies
Hospital Anxiety and Depression Scale (HADS)	65
Beck Anxiety Inventory (BAI)	4
Patient Health Questionnaire (PHQ)	1
Hopkins Symptom Checklist	1
Hamilton Anxiety Scale (HAM-A)	12
Spielberger State Trait Anxiety Inventory (STAI)	15
General Health Questionnaire (GHQ-28)	1
General Health Questionnaire (GHQ-30)	1
Yale-Brown Obsessive Compulsive Scale	1
Neuropsychology Inventory (NPI)	1
Health Anxiety Inventory	2
Profile of Mood States (POMS)	2
Mental Health Inventory (MHI)	2
Social Phobia Inventory (SPIN)	2
Depression Anxiety Stress Scale (DASS)	2
Crown-Crisp Experiential Index (CCEI)	1

Nottingham Adjustment Scale (NAS)	2
Zung Self-Rating Anxiety Scale (SAS)	1
Zung Anxiety Rating Scale (ZARS) (German)	1
Symptom Checklist-90 (SCL-90) (adapted to Spanish)	1
PROMIS	3
DSM	3
ICD	2
K-SADS	1
Determined by Psychiatrist	2
Clinician administered PTSD scale	1

Appendix C. Results and Strengths of Associations for Cross-Sectional and Prospective Studies

Cross-Sectional Studies

Authors, Year	No. Patients	No. Controls	Factor/s investigated	Type analysis	Results
Akbar, N., et al. (2011)	108	0	Cognitive dysfunction	Stepwise linear regression model	Anxiety was a predictor for cognitive dysfunction (R^2 = 0.108, F = 12.4 p = 0.001) (measure completed by informant of the patient) (R^2 = 0.272, F = 38.93, p < 0.001) (measure completed by patient).
Al-Asmi, A., et al. (2013)	57	53	Prevalence	Chi-Square; ANOVA; Wilcoxon Rank test	Prevalence = 50.8%. multiple sclerosis was associated with substantial risks of symptoms of anxiety (OR = 2.43; 95 % CI 1.13, 6.82; P = 0.03). HADS scores on anxiety among MS patients were significantly higher (8.3 vs. 4.9) than that among the control group (P = 0.04).
Aloulou, J., et al. (2011)	31	0	Disability; Age; Alexithymia; Depression	Descriptive statistics and correlation analysis	Prevalence = 52%. Anxiety was correlated with the level of disability and age of disease onset. A positive correlation was also found between anxiety and alexithymia and anxiety and depression. (Only abstract available)
Anhoque, C. F., et al. (2011)	19	0	Prevalence; Disability	Correlation analysis	MS patients had a high prevalence of anxiety. The association between anxiety and level of disability was significant (p=0.02) (no strength specified).
Askari, F., et al. (2014)	180	0	Depression; Level of disability	Multiple Regression Analysis	Depression (b=0.61, 95% CI (0.53, 0.8) p=0.001) and level of disability (b=0.38, 95% CI

					(1, -3.3) p<0.001) were significant predictors of anxiety in PwMS.
Bamer, A. M., et al. (2008)	1271	0	Prevalence; Clinical variables	Multiple Logistic Regression	Prevalence =25%. Regression analysis showed that anxiety is associated with difficulties in thinking, higher depressive symptoms, more pain, increased level of stress, sleep problems, not using a wheel chair and with better health. (Only abstract available)
Beier, M., et al. (2013)	513	0	Measure of anxiety and related factors	EFA/CFA and Correlations	The reliability and validity of the PHQ-A as a measure for PwMS was supported for PwMS. The PHQ-A was highly correlated with anxiety(r = .70). Age (r = -.12) and duration of MS (r = -.14) were both negatively associated with anxiety (both p < .005). Women endorsed significantly higher anxiety than men (t (508) = 2.13, p = .03). There were also significant differences in anxiety between MS types; PwMS with SPMS endorsed the most anxiety symptoms (F (3, 496) = 55.4, p = .001). Individuals higher in anxiety also endorsed more depressive symptoms (.70, p < .001), reported higher pain severity (r = .40) and more pain interference (r = .42), (all p < .001). (Only abstract available)
Beiske, A. G., et al. (2008)	140	0	Pain; Fatigue; Age	Multiple Regression Analysis	Pain (OR=5.120, 95%CI (1.087-24.122), p = 0.010), fatigue (OR=0.993, 95% CI (0.882-0.986), p = 0.039) and younger age at onset (OR=0.93, 95% CI 0.88–0.99) p= 0.014) were significant predictors of anxiety. OR=Odds Reduction.
Bogart et al (2015)	106	0	Disability identity, depression,anxiety, MS duration, demographics	Hierarchical regressions	37% had likely cases of anxiety. Stronger disability identity was associated with significantly lower anxiety and explained a significant 4% increase in variance. The significant predictors of anxiety in the final model were age, disability identity, and ADL. The final model explained 19% of the variance in participants' anxiety.
Brajkovic, L., et al. (2009)	68	0	Prevalence, Coping mechanisms	Multiple Regression Analysis	Prevalence = 63.2% (symptoms of anxiety) Predictors improving anxiety were positive reinterpretation, social emotional support and humor; Predictors worsening anxiety were planning, acceptance focus on emotional ventilation and denial. (Only abstract available)
Bruce, J. M. & P. Arnett (2009)	50	45	Depression, Level of disability, Fatigue, Sleep	Correlations	High level of anxiety was correlated with higher levels of depression (r =0.73, p < .001).

			Disturbances		No significant relationships were found between anxiety and disability level, overall fatigue, sleep disturbance, pain, and neuropsychological functioning.
Bruce, J. M., et al. (2009)	79	0	Cognitive impairment and Perceived memory failures.	Stepwise Linear Regression	PwMS reported more anxiety than controls (32.75 + 6.54; t (96) =2.59, p < .05). Self-reported memory problems (r =0.50, p<.001) and higher total dissociation (disruption to cognitive processes) (r = 0.59, p< .001) were correlated with high level of anxiety. Anxiety did not account for unique variance in self-reported memory in the regression model.
Bruce, J. M. & Lynch, S. G. (2011)	85	20	Personality	Stepwise Regression	Stepwise regression revealed that anxiety accounted for unique variance in neuroticism (R^2=0.65, F=153.09, p<0.001) and in conscientiousness (R^2=0.23, F=25.37, p<0.001).
Chalfant, A. M., et al. (2004)	58	0	Prevalence PTSD	Descriptive Statistics	Nine PwMS (16%) met symptom criteria for PTSD.
Chalk, H. M. (2007)	329	0	Gender; RRMS type	MANCOVA	Females (F (1,312) =5.20, p < .05) and patients with RRMS had higher levels of anxiety (F (1,312)= 5.08, p <0.05).
Chylova, M., et al. (2009)	223	0	Age; Health status	Multiple Regression analysis	Anxiety was related to worse physical and mental health status in younger MS patients, but not in the older ones (Only abstract available)
Cihelkova, S. & Bojar, M. (2009)	40	0	Prevalence	Descriptive Analysis	A high prevalence of anxiety was detected by BAI II of 65% and by SCL-90 of 62 % in PwMS (Only abstract available)
Counsell, A., et al. (2013)	126	0	PTSD	Multiple Regression analysis	Higher MS-related disability (b=0.15, p=0.007), having another health condition (b=2.48, p=0.005) and anxiety (b=1.35, p=0.000) were significant predictors of PTSD symptoms (R^2=0.51).
Curral, R., et al. (2011)	48	0	Prevalence	Descriptive Statistics	PwMS did not have significantly high levels of anxiety (Only abstract available)
Da Silva, A. M., et al. (2011)	325	183	Prevalence; Gender; Education.	Correlation analysis; MANCOVA	Prevalence =51%. Anxiety scores were significantly higher for women (t=4.213, p < 0.001). Negative correlations were found between number of years of education and level of anxiety (r = − 0.215 and p < 0.001). For MANCOVA no statistically significant differences were found between anxiety and course of illness.
Dahl, O. P., et al. (2009)	172	56,000	Gender; Duration; Disability	Descriptive statistics and	Among men the prevalence rate of anxiety was 31.1%

				correlation analysis	versus 12.1% for controls (p = 0.002). For women, the prevalence of anxiety was 29.7% versus 17.4% for controls (p < 0.001). Anxiety was not correlated with duration of disease or disability.
Dubayova, T., et al. (2013)	198	142	Quality of life	Multiple Regression Analysis	Anxiety was a significant predictor for lower scores for quality of life in the regression model (b=0.38, p<0.001, R^2=0.33)
Espinola-Nadurille, M., et al. (2010)	37	37	Prevalence of anxiety; Depression	Descriptive Statistics	Prevalence = 28.6%. Levels of anxiety were significantly higher in patients with depressive disorders compared to those without (21.2 SD=9.91 versus 9.33 SD=8.54, p.001). No significant differences concerning correlations between age, number of relapses, duration of illness, disability and anxiety were found.
Etesam et al. (2016)	112	0	Self-disclosure; Depression	Pearson Correlation coefficient Multiple Regression analysis	There was a positive and significant correlation among disease variables (level of disability and the number of times hospitalized) and anxiety (p<0.01.) Higher scores of anxiety were negatively associated with distress disclosure (p<0.01.). Multiple linear regression analysis revealed that frequency of hospitalization and disability level, predicted anxiety (p<0.05.) Controlling disease variables demonstrated distress disclosure as an independent factor to predict anxiety in the participants (p<0.05.)
Farrell, E., et al. (2011)	101	0	Prevalence; Cognitive Difficulties; Depression	Correlation analysis	Prevalence = 32.1%. There were significant correlations between anxiety and reported cognitive difficulties and anxiety and depression. (Only abstract available)
Feinstein, A., et al. (1999)	152	0	Prevalence; Gender	Descriptive Statistics	Prevalence =15.8%. Anxious patients were statistically more likely to be female (22/24 were female).
Fisk, J. D., et al. (2014)	949	0	Quality of life	Multiple Regression Analysis	Regression analyses showed that anxiety was associated with quality of life (Only abstract available)
Foroughipour, M., et al. (2012)	112	0	OCD	Chi-Square tests	Prevalence of OCD in patients with MS was 16.1%. The OCD was significantly associated with a higher level of disability (X-2 = 86.515, p = 0.0001), duration of disease (X^2= 9.135, p= 0.033), phenotypic subgroup (X^2 = 8.970, p = 0.029), cranial nerve involvement (X^2 = 6.531, p= 0.011), cerebellar nerve involvement (X^2 = 19.390, p=

					0.0001), autonomic nerve involvement (X^2 = 18.587, p = 0.0001), sensory nerve involvement (X^2 = 11.593, p = 0.001) and motor nerve involvement (X^2 = 25.652, p = 0.0001).
Fruhwald, S., et al. (2001)	74	74	Quality of life	Mann Whitney-U tests	There was a significant relationship between anxiety and quality of Life (Only abstract available in English).
Garfield, A. C. & Lincoln, N. B. (2012)	157	0	Prevalence; Difficulty with mood; Distress; Depression	WALD Chi-square test Logistic Regression	Prevalence =57%. Experiencing difficulty with mood (Wald's X^2 (1) = 11, b=1.18, p= 0.001), psychological distress (Wald's X^2 (1) = 6.3, b=0.21, p = 0.01) and depression (Wald's X^2 (1) = 5.05, b=0.28, p =0.03) were significant predictors of clinically significant levels of anxiety (R^2=0.46).
Glanz, B. I., et al. (2012).	377	0	Presenteeism	Correlation Analysis	Presenteeism was correlated with anxiety (r=0.39, p<0.05).
Goretti, B., et al. (2014).	190	0	Cognitive Dysfunction	Multiple Regression Analysis	In the multivariate analysis, anxiety was associated with failure on the Symbol Digit Modalities Test (OR = 2.07, 95 % CI 1.01–4.41, p = 0.05), There was no relationship between anxiety and failure on other neither neuropsychological tasks nor overall cognitive dysfunction.
Grech et al (2015)	107	0	Cognitive Dysfunction; stress, depression; Quality of life	Hierarchical regression analysis	Only the self- and independent-report variables significantly predicted trait anxiety (DEX–S: B = 0.72,p=.008,OR=2.06;DEX–I:B=0.41,p= .04, OR = 1.51). They were entered into the final model jointly at Step 2, where they significantly predicted trait anxiety, although only the DEX–S individually reached significance, B = 0.64, p = .03, OR = 1.89. The total model accounted for 29.0% of the variability in trait anxiety.
Hakim, E. A., et al. (2000).	305	0	Prevalence; Gender; Age; Duration; Severity	Standardised Prevalence Ratios	Prevalence =16%. Anxiety was not related to disease severity, duration or gender. Anxiety was present in 37% of patients who were less than 30 years old compared to 17% of those in the age group 30 to 44 years.
Harding, K. E., et al. (2012).	102	0	Age	Correlation analysis	There was no evidence for increased levels of anxiety in the younger onset MS group (Only abstract available)
Ionescu, P., et al. (2012).	112	0	Level of disability; Depression; Daily functioning; Quality of life;	Pearson and Kendall methods.	Level of disability, depression, daily functioning and quality of life were all strongly correlated with anxiety (p = 0.0001) (Only

					abstract available).
Iriarte, J., et al. (2000).	155	0	Fatigue	Kruskal Wallis H test	Anxiety was associated with fatigue (Kruskal H=7.59, P<0.005).
Janssens, A., et al. (2003).	101	101	Prevalence of anxiety	ANOVA	Prevalence =34% (eight months after diagnosis)
Janssens, A., et al. (2004).	101	0	Prevalence; Level of disability; Risk perception	Multiple Regression Analysis	Prevalence =34%. Higher level of disability reported by PwMS was a significant predictor for anxiety symptoms (b= 0.24, p =.002). Perceived 2-year risk was also a significant predictor for anxiety (b=0.78, p<0.001).
Jones, K. H., et al. (2012)	4178	0	Prevalence of anxiety; Age; Time since diagnosis; Depression; MS type	Kruskal-Wallis, ANOVA	Prevalence =54%. There was a weak negative relationship between age and anxiety score (rho = 20.18, p <0.001) and between time since diagnosis and anxiety score (rho = 20.10, p<0.001). Depression and anxiety scores were positively correlated (rho = 0.565, p<0.001). Anxiety was most frequent among people with RRMS (56.5%). Anxiety scores were higher in women (p<0.001, N = 4287). There was no significant difference in anxiety scores between the genders for SPMS (not sig, N = 396). Kruskall-Wallis tests showed that there was no significant difference in men's anxiety scores for different types of MS (not sig, N = 1226). However, women's anxiety scores differed with type of MS (p = 0.017, N = 2998), with the highest levels in RRMS.
Jones, K. H., et al. (2013)	4500	0	Prevalence	Descriptive Analysis	There was a high prevalence of anxiety in PwMS (Only abstract available)
Jones, S. M. & Amtmann, D. (2014)	405	0	Healthcare worry	Multiple Regression Analysis	Total level of health care was found to be a significant predictor for anxiety (b=0.363, p<0.01, R^2 =0.184)
Jones, K. H., et al. (2014)	4 516	0	Level of disability; Gender; Durations; Age	Multiple Regression analysis	Level of disability (b= 0.398), male gender (b=20.076), PPMS (b=20.062), disease duration (b=20.080), and age (b=20.218) (all p<0.001) were all significant predictors of anxiety. This indicates that level of disability is the major contributor to the increase in the anxiety score, and that the other factors actually reduce the effect, with age being the most important of these (R^2=0.184; Durbin-Watson 1.984; ANOVA F=161.508, df=5, p<0.001).
Jopson, N. M. & Moss-Morris, R.	168	0	Illness representations	Hierarchical Multiple	Illness identity (b=0.20. p<0.05), cyclical timeline

(2003)				Regression Analysis	(b=0.23, p<0.05) and illness coherence (b=0.18, p<0.05) (all types of illness representations) were all significant predictors of anxiety (R^2 =0.23).
Julian, L. J. & Arnett, P. A. (2009)	77	0	Cognitive functioning	Multiple Regression Analysis	Cognitive functioning in MS was a significant predictor for anxiety in the regression model F (1, 68)=4.53, p<0.05 (R^2 =0.35).
Karadayi, H., et al. (2014)	31	31	Disability; Fatigue; Depression; Cognitive Impairment	Correlations	Anxiety was significantly correlated with level of disability (r=0.69, p<0.01), depression (r=0.43, p<0.01) and fatigue (r=0.49, p<0.01). Anxiety was not correlated with cognitive impairment.
Kehler, M. D. & Hadjistavropoulos, H. D. (2009)	246	0	Health anxiety and coping	Logistic and Hierarchical Regression	Prevalence =28%. Anxiety did not significantly differ among individuals with different types of MS (F (2, 210) = 1.10, ns). Emotional Preoccupation coping was found to be a significant predictor for anxiety (R^2 =0.40, F(1,227)=152.90, p<.001). Participants with high health anxiety were 1.38 times more likely to have high generalized anxiety. Health anxiety and generalized anxiety demonstrated a strong positive correlation (r (231) = 0.67, p < 0.001).
Kikuchi, H., et al. (2013)	163	0	Employment	Structural Equation Modeling	Changes in employment status after MS onset were negatively associated with anxiety (b=-0.25, p<0.05)
Korostil, M. & Feinstein, A. (2007)	140	0	Prevalence, Gender, Depression, Drinking; Social stress; Suicide	T-tests and Discriminative Function Analysis	Lifetime prevalence of any anxiety disorder= 35.7%. Prev. panic disorder = 10%, OCD= 8.6%, and GAD=18.6%. Subjects with an anxiety disorder were more likely to be female (t (1) =7.7, p=0.06), have a history of depression (t (1)=22.0, p=0.001), drink to excess (t (1)=4.7, p=0.03), report higher social stress (t (1)= 3.6, p=0.001) and have contemplated suicide (t (138)=3.6, p=0.04).
Kostaras, P., et al. (2008)	60	0	Cognitive deficits	Correlations	No correlation was established between anxiety and cognitive dysfunction (Only abstract available)
Kraft, G. H., et al. (2012)	1,543	0	Prevalence	Descriptive Statistics	There was a higher prevalence of anxiety in PwMS in comparison to healthy controls (p<0.001) (Only abstract available)
Krokavcova, M., et al. (2010)	184	0	Employment	Stepwise Logistic Regression	Patients without anxiety were 2.64 times more likely to be employed. Not suffering from anxiety was a significant predictor of employment status

					(b=0.972, 95%CI: 1.23-5.67, p=0.012).
Labuz-Roszak, B., et al. (2007)	122	0	Prevalence; Fatigue	Correlation Analysis	Prevalence =26.2%. An association was found between anxiety and fatigue (Only abstract available)
Leonavicius, R. & Adomaitiene, V. (2013)	312	0	Prevalence; Gender; Age, Duration, Depression; level of social activity.	Logistic Regression	Prevalence =20.2%. Anxiety was found to be higher among females (22.4%vs 16.4%). Younger age (b=2.357, p<0.05), shorter MS duration (b=11.904, p<0.05), depression (b=17.283, p<0.05) and few MS group activities (b=8.222, p<0.005) were significant predictors of anxiety. Being socially active was not a significant predictor of anxiety among PwMS.
Leonavicius, R. & Adomaitiene, V. (2011)	270	0	Prevalence; Duration Depression	Odds Ratios	Prevalence =17%. Patients with shorter MS duration (<10 years) had 2.52 times higher odds ratio to be diagnosed with anxiety. Patients with depression had 3.03 times higher odds ratio to be diagnosed with anxiety (Only abstract available).
Leonavicius, R. & Adomaitiene, V. (2014)	137	0	Prevalence; Sleep disturbances	Multivariate Linear Regression	Prevalence =19.7%. Sleep disturbances were found to be a significant predictor anxiety (b=3.362, CI 95% (1.113, 5.885)
Lester, K., et al. (2007)	82	0	Level of disability; Cognitive impairment;	Hierarchical Regression Analysis	Level of disability (b=0.46) and cognitive impairment (b=0.46) were both significant predictors of anxiety ($p<0.005$, $R^2=0.39$)
Levinthal, D. J. & Bielefeldt, K. (2014)	71	0	Dyspeptic symptoms	F-tests, Fisher Exact Tests	PwMS patients with moderate to severe dyspepsia had higher anxiety compared to controls (62.5%vs. 27.3%) (Only abstract available)
Liu, X. J., et al. (2009)	41	0	Negative life events; Personality	Correlation analysis	There were higher levels of anxiety in PwMS than controls (p<0.001). Significant correlations were found between anxiety and negative life events (r=0.258), problems of family life (r=0.254) (both p<0.01), social functioning (r=0.247, p<0.05), extroversion (r=--0.296) and neuroticism (r=0.380) (both p<0.001).
Lopes, J., et al. (2012)	119	0	Prevalence; Fatigue	Correlation analysis	Prevalence =44.5%. Fatigue was associated with anxiety (OR 8.33, 95%CI 2.33-29.75, p < 0.001) (Only abstract available)
Maia, D., et al. (2011)	25	0	Neuropsychological functioning	Correlation analysis	There was no significant relationship between neuropsychological functioning and anxiety (Only abstract available)
Marrie, R. A., et al. (2013)	4192	20,940	Prevalence of anxiety	Descriptive Analysis	Prevalence =35.6%
Medin, K. L., et al. (2014)	13	0	Epilepsy	Correlation analysis	Of those diagnosed with MS and epilepsy, 77% had clinically significant levels of anxiety (Only abstract available)

Middleton, L. S., et al. (2006)	221	0	Perception global functioning	Multiple Regression Analysis	Anxiety was found to significantly predict perceptions of global cognitive functioning (b = .55; *t* = 8.16; p < .001) but not objective cognitive performance.
Milanlioglu, A., et al. (2013)	50	30	Coping strategies	Correlation analysis	There was a positive correlation with substance use and non-functional coping strategies for anxiety (no strength specified in paper).
Milinis, K., et al. (2014)	260	0	Spasticity	Correlation analysis	There was a weak correlation between anxiety and spasticity (r=0.23,p< 0.05). (Only abstract available)
Miljatovic, A. M. (2013)	98	0	Level of disability	Correlation analysis	A strong correlation was found between anxiety and level of disability (p= 0.0001). (Only abstract available)
Mills, R. J. & Young, C. A. (2011)	635	0	Fatigue	Linear regression	High levels of anxiety were associated with greater fatigue (rho=0.426, mean difference 1.30 logits, 95% CI 0.99–1.61, p < 0.001, R^2 <0.3).
Montel, S. R. & Bungener, C. (2007)	135	0	Coping; Pain; Distress; Sleep	ANOVA	Prevalence anxiety= 4%. Anxiety had a significant effect on emotional coping strategies (WCC: p =0.005; CHIP: P<0.001). In the AVOVA, anxiety was negatively related to pain (-0.44), emotional well-being (-0.52), distress (-0.39), cognitive functions (-0.42), general well-being (-0.35), and sleep (-0.31). WCC=Ways of Coping Checklist. CHIP=Coping with Health Injuries and Problems.
Morrow, S. A., et al. (2014)	96	0	Prevalence	Descriptive statistics	Prevalence =24% (Only abstract available)
Nicholl, C. R., et al. (2001)	96	0	Prevalence; Disability	Correlation analysis	Prevalence =31%. There was a correlation between level of disability and anxiety (r=0.49, p<0.01)
Niino, M., et al. (2012)	163	0	Employment; Knowledge; Disability	Structural Equation Modeling	Level of disability was not associated with anxiety. Changes in employment status after onset of MS increased anxiety. Knowledge of disease information improved level of anxiety (Only abstract available).
Noy, S., et al. (1995)	20	0	Exacerbations; Duration	Correlations	Anxiety level was positively correlated with number of exacerbations (r=0.39 p=0.08) but not with disease duration.
Ostacoli, L., et al. (2013)	232	0	PTSD	Multiple Linear Regression	Prevalence =5.17 % for PTSD. Levels of education (0R=0.672, 95% p=0.019) anxiety (0R=1.474, p=0.016) and depression (0R=1.398, 95% p=0.022) were significant determinants of the presence of PTSD.
Paredes, S. & Kirchner Nebot, T. (2012)	90	0	Gender; Time since diagnosis	Correlation analysis	High levels of anxiety were present in both genders. There was no relationship between anxiety and time since diagnosis (Only abstract available).

Pfaff, L., et al. (2014)	16	16	Level of disability	n/s (bivariate)	Level of disability was associated with anxiety (p=0.03) (Only abstract available)
Pieper, L., et al. (2012)	50	0	Prevalence; Disability	n/s (bivariate)	Lifetime prevalence of any anxiety disorder =53.2% Anxiety was not associated with level of disability (Only abstract available).
Poder, K., et al. (2009)	245	0	Social Anxiety	Correlation analysis	Prevalence of social anxiety= 30.6% (SPIN). There was a strong correlation between social anxiety and generalized anxiety (r=0.59, p<0.01) and social anxiety and depression (r=0.56, p<0.01). Severity of social anxiety symptoms was correlated with reduced health-related quality of life (r=-0.40, p<0.01) and not related to neurological disability
Poder, K., et al. (2007)	265	0	Social Anxiety	Multivariate Models	Prevalence of social anxiety=29.8% (SPIN) and 22.4% (MINI SPIN). Gender, age, EDSS and use of disease modifying drugs did not differ between groups with and without social anxiety. Those with social anxiety had lower health related quality of life scores (p<0.001) (Only abstract available).
Reade, J. W., et al. (2012)	145	0	Stress; Social support	ANOVA	Anxiety levels were significantly associated with high level of stress and lower levels of social support (F (3, 125)=14.23, p<0.001).
Roy Bellina, S., et al. (2010)	32	0	Number of symptoms	Correlation analysis	A positive correlation was found between "the number of symptoms inherent to the disease" and anxiety (r=0.59, p=0.0004) (Only abstract available)
Roy-Bellina, S., et al. (2009)	45	0	Coping strategies	Correlation analysis	Problem-focused coping was negatively correlated with anxiety (state: r=-0.410, p=0.0048; feature: r=-0.458, p=0.0013). Emotion-focused coping was positively correlated with anxiety (feature: r=0.554, p=0.0001) (Only abstract available).
Sarisoy, G., et al. (2013)	76	76	Prevalence; Disability	Correlation analysis	There was a high prevalence of anxiety in PwMS compared to the healthy controls. Level of disability and high level of anxiety were correlated (r=0.355, p=0.002).
Schwartz, C. E., et al. (1996)	139	0	Fatigue	Multiple Regression Analysis	Anxiety was not a predictor for fatigue in the regression model.
Shabani, A., et al. (2007)	85	0	Prevalence	Chi Square tests	Prevalence of all anxiety disorders=22.4%. Prevalence of OCD was significantly higher compared to controls (p<0.05). Prevalence of GAD= 11.8%, panic disorder = 1.2%, specific phobias=7.1% and OCD=11.8%. There was a significant association between anxiety and university education (p<0.05, df = 1, F^2 = 13.99).

Sidorenko, T., et al. (2010)	148	0	Prevalence; Adherence	n/s (bivariate analysis)	PwMS had higher levels of anxiety than controls (38,5% Vs. 19,5% respectively; p<0.05). Low adherence was associated with high anxiety (Only abstract available).
Silva, A., et al. (2009)	231	0	Course of illness	n/s (bivariate analysis)	Level of anxiety was significantly higher in patients than controls (p<0.001). No significant differences for anxiety were found during course of illness (Only abstract available).
Silva, A. M., et al. (2011)	159	0	Quality of life	ANCOVA	QoL was predicted by anxiety (Benign MS: F=4.39, p=0.045; Non-Benign MS: F=12.704, p=0.001) (Only abstract available).
Simpson, R. J., et al. (2014)	3826	1,268,859	Prevalence of anxiety	Odds ratios	Anxiety was the 2nd highest comorbid mental health condition for PwMS (OR=3.18).
Smith, S. J. & Young, C. A. (2000)	88	0	Prevalence; Depression; Perception of disability	Descriptive statistics	Prevalence =34%. Depression was associated with anxiety in two-thirds of depressed patients. There was no association between anxiety and perception of disability.
Spain, L. A., et al. (2007)	580	0	Prevalence; Quality of life	Regression Analysis	Prevalence =34%. Anxiety was found to be a significant predictor for quality of life as indicated under the following QoL sub-scales: anxiety predicted physical functioning (b=.0.19, p<0.05), bodily pain (b=-0.19,p<0.01), general health (b=-0.13, p<0.05), vitality (b=-0.12, p<0.05), social function (b=-0.12, p<0.05), emotional functioning (b=-0.42, p<0.01) and mental health (b=0.5, p<0.001).
Stenager, E., et al. (1994)	94	0	Cognitive Dysfunction; Course of illness	Correlation analysis	Level of disability was correlated with anxiety (F-Test=2.61, p < 0.05; df. 1.92). Trail Making (cognitive functioning) was also correlated with anxiety (no strength specified). No significant correlation was found between the course of illness and State anxiety (F= 1.73; p=0.18, d.f. 1.92) and Trait anxiety (F=0.18; p=0.84, df. 1.92).
Suh, Y., et al. (2010)	96	0	Prevalence; Physical Activity	Correlation analysis	Prevalence =41%. Physical activity was not correlated with anxiety (r = -0.021; p>0.05).
Szilasiova, J., et al. (2011)	114	0	Prevalence; Quality of LIfe	Multiple Linear Regression	Prevalence =27%. Anxiety was found to be a significant predictor of QoL (b=–0.51, p < 0.001, R^2 =0.613)
Tadic, D. & Dajic, V. (2013)	50	0	Quality of life	Correlation Analysis	A strong correlation was found between high anxiety and overall QoL (r=-0.674, p< 0.001)
Tan-Kristanto et al (2015)	129	0	Resilience, self-efficacy, coping styles; depression	Pearson's correlation; hierarchical regres- sion	Denial (b=0.29, p < 0.001), level of disability (b=0.23, p < 0.05) and lower levels of personal competence (b=-0.26, p < 0.05) were

				analyses	independent significant predictors of the anxiety score (R^2 = 0.364)
Theaudin et al (2016)	711	0	Depression; Gender	Linear regression analysis.	Higher HADS anxiety scores in females (t = −4.555, p < 0.001),52.1% of females and 37.8% of males were deemed clinically anxious (HADS anxiety ⩾ 8; χ^2 = 12.532, p < 0.001). A gender com- parison of depression together with anxiety revealed higher frequencies of both these symptoms in women than in men (32.3% of females depressed and anxious vs. 23.4% of males, χ^2 = 5.795, p = 0.02).
Thornton, E. W., et al. (2006)	39	40	Self-efficacy; Worry	Correlation analysis	Anxiety was significantly correlated with self-efficacy and worry(r=0.59-WQMS) (r=0.77-PSWQ)(both p<0.01).
Tsivgoulis, G., et al. (2007)	86	0	Level of disability; Level of education	Multiple Linear Regression Analyses	Level of disability (b=+0.430, p < 0.001) and level of education (b =-0.235, P < 0.041) were significant predictors for anxiety. These accounted for 18.5% (R^2 = 0.185) and 5.5% (R^2 = 0.055) of the variance in anxiety. Initial association between education and anxiety failed to retain statistical significance in the multiple linear regression analyses performed both with the backward and forward procedure (unstandardized linear regression coefficient: -0.471; 95% CI -1.170 to 0.228; b= -0.143; p= 0.184).
Uca et al (2016)	55	56	Prevalence; Personality disorders; Depression	*t* test; Mann-Whitney U test c^2test/ Fisher's exact test	38% had an anxiety disorder. MS patients with any personality disorder had significantly higher frequency of GAD (p=0.008), any anxiety disorder (p=0.005), and post-traumatic stress disorder (p=0.037),
Uguz, F., et al. (2008)	74	0	Anxiety subtypes; Exacerbation; Disease duration	Logistic Regression Analysis	Prevalence rate for GAD= 18.9%, specific phobia=18.9% and OCD=14.9%. The predictors of any anxiety disorder were presence of the exacerbation phase of MS (B =-1.233, Wald x^2 =5.603, df 1, p=0.018) and shorter disease duration (B=-0.137, Wald x^2=4.376, df 1, p=0.036).
Van Der Hiele, K., et al. (2014)	44	0	Employment	Correlation analysis	There was no correlation between employment and anxiety symptoms.
Van Der Hiele, K., et al. (2010)	128	0	Subjective cognitive functioning	Correlation analysis	Participants with subjective executive problems had higher anxiety scores (p< 0.001) than

					participants without subjective executive problems. Objective executive performance was not correlated with anxiety (Only abstract available).
Van der Hiele, K., et al. (2012)	715	0	Psychosocial stress	Logistic Regression	Higher psychosocial stress was found to be a significant predictor of higher anxiety scores (b=0.21, CI 95% (1.16, 1.31) p<0.001) R^2=0.22 (Cox and Snell), 0.30 (Nagelkerke); model $\chi^2(6)$=151.3.
Van der Hiele, K., et al. (2012)	114	0	Executive cognitive performance	ANOVA	Patients with MS underestimating their executive cognitive performance had higher levels of anxiety ($F_{2,105}$ = 7.4, p = 0.001).
Visser, L. H., et al. (2009)	708	0	Cognitive complaints	Correlation analysis	PwMS with cognitive complaints had higher levels of anxiety compared to PwMS without cognitive complaints (p< 0.001) (Only abstract available).
Voiticovschi-Iosob, C. & Moldovanu, I. (2013)	54	0	Pain	Descriptive Statistics	Anxiety was associated with chronic pain in 87.8 % of PwMS (Only abstract available).
Vuger-Kovacic, D., et al. (2007)	457	0	Duration	Correlation analysis	Anxiety did not significantly increase with longer duration of MS.
Weisbrot, D., et al. (2012)	45	0	Prevalence	Descriptive Analysis	Prevalence. =44.4% (Only abstract available).
White, C. P., et al. (2008)	145	0	Speech difficulties; Pain; Fatigue; Depression; Health distress	Correlation and Regression Analyses	Anxiety was correlated with speech difficulties (r=.32, p<0.001), pain (r=.34, p<0.001), fatigue (p=.30, p<0.001) and depression(r=.74, p<0.001). It was not predictive of health distress in the regression model with other factors.
Ziegler, K., et al. (2010)	50	0	PTSD	ANOVAS.	12% of the PwMS had a PTSD lifetime diagnosis lifetime and 24% had a PTSD associated with MS-diagnosis. MS-patients with PTSD showed statistically significant lower self-efficacy, sense of coherence and social support (Only abstract available).
Zorzon, M., et al. (2001)	97	110	Biological correlates	Correlation analysis	The anxiety did not correlate significantly with any of the measures of regional and total lesion loads and brain volume.

Results and Strengths of Associations for Prospective Studies

Authors, Year	No. Patients	No. Controls	Factor/s investigated	Type analysis	Results
Bianchi, V., et al. (2014)	39	39	Prevalence and Coping	Multivariable linear regression analyses	Prevalence =53.8%. There were higher scores for anxiety (p < 0.001) in patients compared with controls. 'Accepting responsibility' coping (b = 0.53; p < 0.001) and 'Seeking social support'

					coping (b = 0.22; p = 0.02) were both predictors of anxiety (R^2=0.29). Over the 24-month follow-up, there was a significant reduction in anxiety (p < 0.001). At the end of follow-up, changes in depression and anxiety scores were strongly correlated with eachother (r=0.70, p<0.001). This decrease was also correlated with a decrease in 'Accepting responsibilities' coping scores for anxiety (r = 0.43; p = 0.018).
Brown, R. F., et al. (2009)	101	0	Depression, Immunotherapy; Coping; Optimism	Regression models	Depression (b=1.07, p<0.0001) and baseline immunotherapy status (b=-4.85, p<0.0001) best predicted later anxiety levels, followed by smoking (b=2.5, p<0.003), no relaxation training (b=-2.56, p<0.0011), and low dispositional optimism (b=-0.35, p<0.0017).
Burns, M. N., et al. (2013)	121	0	Exacerbations	Logistic regression	Pseudo-exacerbations were associated anxiety symptoms, t (1072) = 3.19, p = .001. There was a significant main effect of confirmed exacerbations on anxiety symptoms (t (1072) = 2.93, p = .004). Baseline anxiety symptoms were not significantly associated with risk for pseudo- or confirmed exacerbations (ps > .14). Increases in anxiety symptoms relative to baseline predicted subsequent onset of new pseudo-exacerbations (Z = 2.30, p = .02).
Christodoulou, C., et al. (2009)	38	38	Cognitive change; Cognitive Performance	Multiple Regression and Pearson Correlations	Anxiety as a significant predictor of cognitive change (b = -0.569, p <0.01, R^2=0.458). A correlation was also found for anxiety and cognitive performance (r=-0.523, p<0.01).
Dalos, N. P., et al. (1983)	73	23 (Spinal Chord patients)	Relapse	T-tests	There were significant levels of anxiety in PwMS experiencing relapse (p<0.001) compared to controls (no strength of association specified)
Diaz-Olavarrieta, C., et al. (1999)	44	25	Prevalence; Frontotemporal changes	The Kruskal-Wallis test	Prevalence =37%. Anxiety had no significant association with frontotemporal changes measured by the MRI. No associations were found between anxiety and level of disability, gender or age.
Giordano, A., et al. (2011)	197	0	Gender; Depression; Duration	Multivariate Linear mixed model analysis	There was a statistically significant decrease in anxiety score at the six-month follow-up. Multivariate linear mixed model analysis showed that the decrease of anxiety scores over time remained significant (F=4.96, DF(2, 97), p = 0.008) after controlling for clinical variables (disability, depression, duration) and demographic variables (sex, age, education). Of these, female sex (F=15.80, DF (1, 114), p<0.001) and depression (F=24.80, DF (1, 23), p<0.001) each had an independent influence on anxiety.
Hartoonian et al (2015)	513	0	Depression; Time since onset of MS; EDSS; pain; fatigue	Hierarchical regression model	Anxiety (β <.001), employment (β =.07) and non-somatic depressive symptoms (β =.10) at baseline significantly predicted anxiety at time 2, *p*s<.05
Hoang et al (2016)	5084	24771	Depression; antidepressant and anxiolytic	Logistic regression analyses	In the pre-diagnostic period, the OR for having a diagnosis of depression and anxiety is 1.4 (95% confidence interval (CI) =1.05–1.88). In the post-diagnostic period the OR is 1.23 (CI= 0.92–1.64) for

			prescriptions,		depression and anxiety diagnosis.
Janssens, A., et al. (2006)	101	76	Disability; Time since diagnosis	SAS Proc Mixed	Prevalence =34% at baseline, 30% at follow-up. Mean anxiety scores of patients remained higher than controls at all times (all $p < 0.05$). Higher level of disability was associated with higher levels of anxiety in patients (all $P < 0.001$). Time since diagnosis was not associated with levels of anxiety. No association found between anxiety and changes in disability status. Anxiety at baseline correctly identified 55% of the participants with high anxiety at follow-up (sensitivity =55%), and 85% of those who will not develop high levels of anxiety during follow-up.
Johnson, K., et al. (2012)	613	0	Social support	T-tests	The high social support group had a reduction in anxiety scores in contrast to the population norm ($p < 0.001$) (Only abstract available).
McCabe, M. P. (2005)	243	184	Gender, Coping	MANOVA and Regression	No significant sex or sex-group interaction demonstrated significant differences between the groups in levels of anxiety ($(F (2,421)=8.92, P<0.001)$. With all of the variables in the regression equation, anxiety at Time 1 was the only unique predictor for anxiety 18 months later ($F (1,95)=45.47, P<0.001, R^2=.32$). In the non-exacerbation group, coping variables did not explain variance of anxiety. With all of the variables in the regression equation, anxiety at Time 1 was the only unique predictor for anxiety 18 months later ($F(1,149)=73.44, P<0.001, R^2=.33$).
McKay et al (2016)	949	0	Depression; Smoking; Alcohol Dependence; Disability	Pearson χ^2 test/ Fisher's exact test, logistic regression.	Alcohol dependence was associated with increased odds of anxiety (OR: 1.88; 95% CI: 1.37–2.57). The association persisted after adjusting for age, sex, EDSS, and smoking status (OR: 1.84; 95% CI: 1.32–2.58) Smoking was associated with increased odds of anxiety (unadjusted OR: 1.32; 95% CI: 1.05–1.65). When adjusted for age, sex, EDSS, and alcohol dependence, the relationship persisted (OR: 1.29; 95% CI: 1.02–1.63).
Olivares, T., et al. (2012)	50	0	Cognitive and Clinical variables	Pearson Correlations	At baseline there was a correlation between neuropsychological functioning, ($r=0.442, p<.05$), QoL ($r= -.627, p<.001$) and years since onset ($r= -.611, p<.001$) with anxiety. Anxiety symptoms were markedly related with low disease duration. Follow-up measures found fatigue ($r=.472, p<.001$), QoL mental ($r= -.727, p<.001$) and QoL physical ($r= -.518, p<.001$) were correlated with anxiety. Years since onset and neuropsychological performance were not correlated with anxiety at follow-up (Only abstract available).
Pakenham, K. I. & Samios,	69	69	Coping	Multilevel Modeling	Anxiety significantly associated with low acceptance (-0.41) and mindfulness

C. (2013)					(0.40) and high depression (0.68) (all p<0.001).
Pekmezovic, T., et al. (2012)	109	0	Quality of life	T-tests	Baseline scores for quality of life were associated with anxiety (Only abstract available).
Potagas, C., et al. (2008)	37	0	Stressful life events; Relapse	Linear Mixed Model	Zero stressful events are associated with a mean anxiety score of 11.7 (95% CI [10.2–13.1]), one event with an anxiety score of 14.1 (95% CI [12.7–15.4]), two events with an anxiety score of 16.1 (95% CI [14.5–17.8]), three with a anxiety score of 20.3 (95% CI [18.7–21.9]), and four or five events with an anxiety score of 22.2 (95% CI: [20.2–24.1]). In the univariate analysis the risk of a relapse was associated with high level of anxiety (2.9, 95% CI: (1.3-6.4) P=0.008).
Solari, A., et al. (2010)	121	0	Prevalence; Depression; Gender	Multivariate linear regression	Prevalence = 43%. Female gender (p = 0.02) and depression (p < 0.001) were predictors of anxiety (R^2= 0.54; p< 0.001). Anxiety decreased (p < 0.001) between 1 and 6-months (no influence of the intervention). (Only abstract available)
Wood, B., et al. (2013)	198	0	Age; Duration of illness; Level of disability; Depression; Fatigue	Regression analysis	At cohort entry, prevalence = 25.4% Older age at cohort entry was associated with lower prevalence of anxiety (RR=0.88). Disease duration at cohort entry was not associated with risk of prevalent anxiety (p=0.33). A higher disability score was not associated with anxiety (0.75). Anxiety and depression (*r*=0.51) and anxiety and fatigue (*r*=0.25), were correlated. Prevalence of anxiety decreased by 8.1% per year of cohort observation (RR=0.92 (95%CI 0.86–0.98), p=0.009). However this effect was driven by a strong decrease of 14.6% per year among females (RR 0.85 (95%CI 0.79–0.93), *p*<0.001), with no significant change over time in males (RR 1.03 (95%CI 0.90–1.17), *p*=0.77).

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Highlights

- Despite the literature indicating the high prevalence of anxiety amongst PwMS no systematic review has been conducted to date.
- One hundred and thirty one studies and abstracts were included in this review in order to give a comprehensive overview of the physical, cognitive, social and psychological factors associated with anxiety amongst PwMS.
- Due to the high levels of comorbidity with depression, many PwMS are likely to benefit from psychological and pharmacological interventions targeting both anxiety and depression.